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DOCTOR OF PHILOSOPHY

Quantifying the Risk of Beta-Blockers and Non-Steroidal Anti-Inflammatory Drugs in Asthma

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Award date:
2014

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Quantifying the Risk of Beta-Blockers and Non-Steroidal Anti-Inflammatory Drugs in Asthma

Dr Daniel R Morales

In support of the degree of Doctor in Philosophy

2014

University of Dundee

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Abbreviations

ACQ	Asthma control questionnaire
AERD	Aspirin-exacerbated respiratory disease
AHR	Airway hyper-responsiveness
ATS	American Thoracic Society
BMI	Body mass index
BTS	British Thoracic Society
cAMP	Cyclic adenosine monophosphate
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COX	Cyclo-oxygenase enzyme
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular disease
CVS	Cardiovascular
FDA	Food and Drug Administration
FENO	Exhaled nitric oxide
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HADS	Hospital Anxiety Depression Scale
HES	Hospital episodes statistics
ICS	Inhaled corticosteroid
IRR	Incidence rate ratio
ISAC	Independent Scientific Advisory Committee for MHRA research
ISAAC	International Study of Asthma and Allergies in Childhood
LABA	Long-acting beta-2 agonist
LKT	Leukotriene receptor antagonist

LO	Lipoxygenase
LT	Cysteinyl leukotrienes
MD	Mean difference
MG	Milligrams
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NSAIDS	Non-steroidal anti-inflammatory drugs
ONS	Office for national statistics
PC	Provocative concentration
PCAE	Primary care asthma exacerbation
PEF	Peak expiratory flow
PG	Prostaglandin
PMR	Polymyalgia rheumatic
QOF	Quality and Outcomes Framework
RD	Risk difference
SABA	Short-acting beta-2 agonist
SCCS	Self-controlled case series
SD	Standard deviation
SE	Standard error
SMART	Salmeterol Multi-Centre Asthma Research Trial
Th	T-helper lymphocyte
UK	United Kingdom
US	United States of America

Acknowledgments

I would like to thank the following people who have helped me complete this thesis:

- Professor Bruce Guthrie for his support with my original fellowship application, and his continued guidance and encouragement throughout.
- Professor Peter Donnan for his statistical advice and discussions on different epidemiological study designs which have informed this work.
- Professor Cathy Jackson and Professor Brian Lipworth for their guidance and contribution of their specialist knowledge of asthma.
- Dr Virginia Hernandez Santiago for helping to review references as part of the systematic review process.
- Mrs Deborah O'Farrell for her administrative support during the fellowship.
- To staff within the Medicines Monitoring Unit at the University of Dundee for providing access to CPRD data.
- The Division of Population Health Sciences at the University of Dundee for creating an excellent supportive environment within which to work.
- The Chief Scientist Office for awarding me the fellowship to carry out this work and for supporting me during my research training.

I would finally and most importantly like to thank my family, in particular my wife Deborah for her love and support throughout.

Declaration

I declare that I am the author of this thesis and that all of the work it describes has been carried out by me. Professor Bruce Guthrie, Professor Cathy Jackson and Dr Virginia Hernandez Santiago assisted by acting as a second reviewer during the systematic review process. I declare that I have consulted all the references cited in this thesis and that this work has not previously been accepted for a higher degree.

A handwritten signature in dark ink, appearing to read 'DMorales', with a horizontal line drawn underneath the name.

Daniel Morales

Date 15/12/2014

Summary of Contents

Beta-blockers and non-steroidal anti-inflammatory drugs (NSAIDs) are often avoided in asthma over risk of bronchospasm which may vary according to drug selectivity and duration of administration. This thesis attempts to quantify the risk of beta-blocker and NSAID exposure in asthma by synthesising clinical trial evidence and conducting observational studies using linked electronic medical records.

As part of this thesis, three systematic reviews of clinical trials were conducted evaluating: the prevalence of aspirin-exacerbated respiratory disease (AERD); risk of selective NSAIDs/COX-2 inhibitors in people with AERD; and risk of acute beta-blocker exposure in people with asthma. Electronic primary care data from the Clinical Practice Research Datalink (CPRD) was used to define a cohort of people with active asthma, measure the prevalence of beta-blocker and NSAID prescribing, and perform a series of nested case control studies evaluating asthma death, asthma hospitalisation and primary care asthma exacerbations (PCAE). A self-controlled case-series was performed for PCAE as well.

Based upon work in this thesis, the prevalence of AERD in people with asthma was around 9%. Selective NSAIDs triggered respiratory symptoms in 8% of people with AERD whilst no significant changes in lung function or symptoms occurred with COX-2 inhibitors. Acute non-selective beta-blocker exposure caused a significant mean fall in FEV1 of 10%, a significant increase in respiratory symptoms in around 1 in 13 and a non-significant increase in falls in FEV1 of $\geq 20\%$ in around 1 in 9. Acute selective beta-blocker exposure caused a significant mean fall in FEV1 of 7%, significant falls in

FEV1 of $\geq 20\%$ in around 1 in 8 and a non-significant increase in respiratory symptoms in around 1 in 33.

The prevalence of selective beta-blocker prescribing in asthma rose by around 200% over the 12 year period whilst the prevalence of non-selective beta-blocker prescribing rose by around 90%. Changing trends in NSAID prescribing occurred over the 12 year period with COX-2 inhibitors now rarely prescribed. Using the nested case control design, both incident and high-dose non-selective beta-blocker exposure was associated with significantly increased risk of asthma morbidity (hospitalisation and PCAE). In contrast, no significant increased risk of asthma morbidity occurred with any type of selective beta-blocker exposure. Consistent findings were seen for PCAE using the self-controlled case series. No significantly increased risk was seen with different oral NSAIDs apart from weak evidence of an association between asthma death and non-selective NSAID exposure which is unlikely to be causal.

Significant numbers of people with asthma are prescribed beta-blockers and NSAIDs. Evidence from clinical trials and observational studies demonstrate that non-selective beta-blockers significantly increase asthma morbidity with risk appearing to vary according to dose and duration of administration. Although selective beta-blockers have the potential to cause significant changes in lung function, no significant increase in asthma morbidity was observed in observational studies. Although around 9% of asthmatics may be susceptible to NSAIDs, no strong evidence was found to suggest that the current practice of NSAID prescribing increases asthma morbidity. At the same time, COX-2 inhibitors are infrequently prescribed despite apparently being well tolerated by people with AERD.

Chapter 1: Introduction

This section provides a background discussion on asthma and its clinical and wider importance, and the pharmacology of beta-blockers and non-steroidal anti-inflammatory drugs with a specific emphasis on how the pharmacology relates to adverse respiratory effects in asthma. The overall aim of the introduction is to put this thesis into context, with the more specific literature relating to the risks of these drugs presented in chapters 3 to 5 which report systematic reviews.

1.1 Asthma

Asthma is a common chronic respiratory disease characterised by expiratory airflow obstruction and acute exacerbations. Patients with asthma develop symptoms such as wheeze, cough, chest tightness and breathlessness which are traditionally episodic in nature (1, 2). The London physician Henry Salter described the episodic nature of asthma in 1860 as "*Paroxysmal dyspnoea of a peculiar character, generally periodic with intervals of healthy respiration between the attacks*" and highlighted the role of bronchial smooth muscle contraction (3). Since then, knowledge regarding the pathophysiology of asthma has advanced significantly.

Several environmental triggers for asthma exist which act in combination with a person's genetic susceptibility. It is well established that asthma can run in families and that the risk of asthma is significantly increased if people have a first-degree relative affected by asthma (4). Environmental triggers include: allergens such as dust mites, pet dander, pollens, food and moulds; viruses; air pollution; tobacco smoke; occupational irritants; medications including beta-blockers and non-steroidal anti-inflammatory drugs; stress; rhinitis; exercise; and cold (5). Understanding environmental triggers

forms an important part of interventions to help patients alter their lifestyle in an attempt to avoid or manage their individual triggers.

1.2 Chronic airway inflammation

1.2.1 Mediators of chronic airway inflammation

Large numbers of cells and mediators are involved in the inflammatory process in asthma including eosinophils, helper T-lymphocytes, mast cells and macrophages. The airway epithelium acts as a protective barrier and releases inflammatory mediators in response to environmental factors including allergens, pathogens, cigarette smoke and pollution (6). In patients with allergic asthma, inhaled allergen binds to dendritic cells on the airway epithelium causing differentiation of T-helper (Th) lymphocytes into the Th2 phenotype (7). Th2 cells produce cytokines and chemokines such as interleukin (IL) 4, 5 and 13 which in turn cause B lymphocytes to produce immunoglobulin E (IgE) (8). Chemokines are released and recruit inflammatory cells into the airways whilst cytokines coordinate the inflammatory cascade. This Th2 cell-dependent IgE-mediated response activates eosinophils and causes degranulation of mast cells promoting the allergic inflammatory cascade. Key mediators of this cascade include cysteinyl leukotrienes and histamine which are potent bronchoconstrictors released by mast cells, whilst activated eosinophils damage airway epithelium by releasing mediators such as eosinophil major basic protein (9). Once damaged, airway epithelium releases several other mediators which activate Th2 cell-dependent airway inflammation independent of allergens, such as damage associated with microbial or viral infection (10).

1.2.2 Effects of chronic airway inflammation

Asthma affects the large and small airways of the lung including the trachea, bronchi and bronchioles. Airway inflammation can persist and become chronic even though symptoms may be episodic and may lead to the pathophysiological changes associated with asthma. Damage to the airway epithelium leads to epithelial shedding thereby exposing deeper airway structures to environmental stimuli. This contributes to airway hyper-responsiveness through increased allergen penetration and stimulation of exposed sensory nerves leading to smooth muscle hyper-excitability (11). Airway inflammation causes secretion and exudation of proteins from airway epithelium and mucus glands leading to characteristic viscous mucus plugs. Inflammatory mediators are released from damaged airway epithelium and activate inflammatory cells causing proliferation of airway smooth muscle, thickening of the basement membrane and airway smooth muscle hypertrophy and hyperplasia (12). Increased smooth muscle mass reduces airway diameter and contributes to airway hyper-responsiveness by enhancing the force associated with bronchoconstrictor stimuli. The combination of chronic inflammation, epithelial damage, airway smooth muscle proliferation and mechanical stress associated with bronchoconstriction leads to airway remodelling and fibrosis, which in turn contributes to disease development and progression.

1.3 Airway smooth muscle

Under normal circumstances, airway calibre is maintained by the bronchomotor tone in airway smooth muscle. In asthma, control of airway smooth muscle is regulated by complex interactions between inflammatory cells and neural processes (13). Neural processes control bronchomotor tone through the balance of sympathetic and parasympathetic drive mediated by the neurotransmitters adrenaline/noradrenaline and

acetylcholine respectively. In this regard, sympathetic stimulation by catecholamines causes airway smooth muscle relaxation whilst parasympathetic stimulation by acetylcholine causes airway smooth muscle contraction (14). Airway smooth muscle contains no direct sympathetic innervation and sympathetic stimulation is mediated by circulating catecholamines binding to and stimulating pulmonary beta2-adrenoceptors. Stimulation of the pulmonary beta2-adrenoceptors causes stimulatory G-protein activation which in turn activates the enzyme adenylyl cyclase leading to increased levels of the intracellular messenger cAMP and smooth muscle relaxation. In contrast, parasympathetic stimulation is mediated through muscarinic-2 (M2) and M3 receptors, which activate inhibitory G-proteins. These in turn inhibit adenylyl cyclase leading to smooth muscle contraction. This understanding has led to the use of inhaled bronchodilators which stimulate the pulmonary beta2-adrenoceptor causing bronchodilatation and are recommended first line agents for the acute relief of asthma symptoms.

1.4 Diagnosis of asthma

Asthma is a clinical diagnosis, based upon symptoms and the demonstration of reversible or variable airflow obstruction (1, 2). Asthma can be difficult to diagnose due to heterogeneity in presentation, severity and results of different investigations. Lung function testing is routinely performed in patients over the age of 5 with suspected asthma and several different methods for assessing airflow obstruction exist. Spirometry is the most commonly used method to detect and quantify airflow obstruction. A forced expiratory manoeuvre is used to measure forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), with a ratio of FEV1:FVC of less than 0.7 suggestive of airflow obstruction. Reversibility and variability are used to describe

changes in lung function which occur naturally or in response to treatment. The presence of reversibility and variability supports the diagnosis of asthma, however normal results do not exclude the diagnosis of asthma especially if patients are asymptomatic at the time of testing. The amount of FEV₁ reversibility in response to inhaled bronchodilators required for the diagnosis of asthma is 12%, with at least a 200ml change from baseline values (1). These changes are important to differentiate between other causes of airflow obstruction including chronic obstructive pulmonary disease (COPD) which typically results in fixed airflow obstruction. Other methods to measure airflow obstruction include peak expiratory flow which may be used to assess diurnal variability as a measure of reversibility. Diurnal variability is defined by the percentage difference between the highest & lowest peak flow reading with values less than 8% regarded as normal. However, peak flow measurements can underestimate airflow obstruction and poor technique is common, often leading to unreliable measurements. Spirometry is preferred for diagnosis because it is highly reproducible, although peak flow is more useful for monitoring asthma control because it requires no specialised equipment.

In patients with symptoms but without objective airflow obstruction, testing for airway hyper-responsiveness is needed. Airway hyper-responsiveness measures the sensitivity of the airways to direct and indirect airway challenges representing triggers and are typically reported as the dose causing a specific fall in FEV₁ (usually of 20%), often referred to as the provocative concentration (PC). Direct challenges use inhaled histamine and metacholine to directly stimulate receptors on airway smooth muscle causing contraction. The PC₂₀ in response to histamine and metacholine suggestive of a diagnosis of asthma is less than 8mg per ml. In comparison, indirect challenges use

inhaled mannitol and exercise to trigger the release of mediators from inflammatory cells including cysteinyl leukotrienes and histamine which lead to airway smooth muscle contraction (15). Challenge tests have high sensitivity in detecting asthma when people have normal lung function, with direct challenges being more sensitive but less specific than indirect challenges (16, 17). Other non-invasive tests which have been used to detect airway inflammation include sputum eosinophilia count and exhaled nitric oxide levels (FE(NO)). Although not widely available in current routine clinical practice, positive results with several of these tests appear to predict response to inhaled corticosteroid (ICS) therapy in asthma (18, 19).

In summary, asthma is a chronic condition associated with episodic symptoms and exacerbations triggered by a variety of stimuli. The main pathophysiology of asthma involves the complex interplay between chronic airway inflammation and airway hyper-responsiveness mediated in part through the effects of airway smooth muscle tone. This pathophysiology is important for understanding the adverse respiratory effects of beta-blockers and non-steroidal anti-inflammatory drugs (NSAIDs) in asthma discussed later in the thesis. It is important to consider that patients with asthma may have different susceptibility to triggers representing different clinical phenotypes. The diagnosis of asthma is important to understand and evaluate the methods and results used in subsequent chapters.

1.5 Clinical asthma phenotypes

Asthma is a condition with several clinical phenotypes which may vary over time as a result of the underlying pathophysiology of chronic airway inflammation and airway hyper-responsiveness (1). Asthma was traditionally characterised in terms of the type of

symptoms experienced and by severity. Asthma severity is typically defined by clinical factors such as symptoms, lung function, dose or number of medications required in achieving full control and the need for rescue therapy. Asthma has also been defined as allergic or atopic asthma if there is a family history of allergic disease, eczema or rhinitis (20). More recently, cluster analysis in adults has distinguished possible clinical phenotypes using clinical variables such as age of onset, body mass index (BMI), eosinophil count, lung function, gender and symptom scores. Haldar et al. applied cluster analysis to 371 patients with either mild-to-moderate asthma managed in primary care or refractory asthma managed in secondary care (21). Analysis revealed clustering of patient characteristics as follows: early-onset atopic asthma associated with eosinophilia; late-onset non-eosinophilic asthma associated with obesity (predominantly affecting women); and late-onset eosinophilic asthma (predominantly affecting men) (21). In a larger analysis involving 726 patients, Moore et al. generated clusters based around age of onset, the presence of atopy, gender, symptom scores and medication use (22). This analysis revealed clustering of patients into the following early-onset atopic asthma phenotypes: normal lung function and low health care use; normal lung function and increased health care use; and reduced lung function and high health care use. This analysis also revealed an association between late-onset non-atopic asthma and obesity (predominantly affecting women) associated with reduced lung function and high health care use. These studies suggest that asthma has several underlying phenotypes with similar symptoms associated with a different response to therapy and clinical outcomes. Despite this, no consensus exists on whether these phenotypes make any difference to clinical management, especially as most cases of asthma are mild and treated in primary care. As such, clinical phenotyping may be more important for the secondary care management of refractory asthma (23).

1.7 Importance of asthma

1.7.1 Epidemiology

Asthma is a common chronic respiratory disease affecting millions of people globally. In 2004, 300 million people were estimated to have active asthma worldwide (24). The largest standardised study estimating the global prevalence of asthma is the International Study of Asthma and Allergies in Childhood (ISAAC). This was a cross-sectional self-reported questionnaire survey conducted between 2000 and 2003 among 106 centres in 56 countries around the world. The study involved 193,404 children aged 6-7 years and 304,679 children aged 13-14 years (25). The global prevalence of asthma symptoms (defined as wheeze in the last 12 months) in the 13-14 year age group was 14.1%, of which 6.9% had symptoms of severe asthma (defined as 4 or more attacks of wheeze, ≥ 1 night per week with disturbed sleep or ≥ 1 episode of wheeze affecting speech in the previous year) (26). Figures for the 6-7 year age group were 11.5% and 4.9% respectively. This study also demonstrated significant geographical variation in the prevalence of asthma with English speaking countries having a higher prevalence of symptoms. The prevalence of current wheeze and lifetime prevalence of asthma in the United Kingdom for children aged 13-14 was 27.1% and 22.9% respectively (27). In reality, determining the true prevalence of asthma is difficult because of heterogeneity in investigation results and the interpretation and recognition of symptoms between countries. In addition, wheeze may be due to other conditions and is not diagnostic of asthma which may limit interpretation of self-reported questionnaire surveys based upon symptoms.

One UK based study has investigated the incidence and prevalence of clinician-diagnosed asthma among children and adolescents using routine electronic healthcare

data from primary care. The 18-year prevalence of clinician-diagnosed asthma among 24,112 children followed from birth was 25.2% for boys and 20.2% for girls, with an overall prevalence of 22.9% (28). However, asthma prevalence is known to peak in childhood and subsequently falls in adulthood (29). In this regard, routine primary and secondary healthcare data have provided national statistics on the prevalence of asthma in Scotland. Using data from around 60 Scottish general practices, the estimated prevalence of asthma in Scotland in 2011 to 2012 was 5.0% (4.3% for men and 5.6% for women) (30). This estimate used a definition of patients consulting for asthma in the last year and may therefore reflect patients more likely to have active asthma. The UK Quality and Outcomes Framework (QOF) are evidence-based indicators used to measure achievement of general practitioners in the UK and include asthma quality indicators (30). Using data contained in QOF registers for asthma, the prevalence of asthma in Scotland in 2011 to 2012 was 6.0%, a figure which is based on the number of people with an asthma Read Code ever recorded prescribed an asthma-related drug in the previous twelve months. In comparison, it is estimated that 8.2% of adults and 9.5% of children in the US have asthma (31).

1.7.2 Economic impact

Asthma causes a large number of scheduled and unscheduled healthcare visits and is associated with a high economic burden. Costs associated with asthma can be divided into direct and indirect costs. Direct costs include hospitalisation, emergency department visits, medication costs, diagnostic tests and education. In contrast, indirect costs typically include the number of school or work days lost and lost productivity associated with traveling, waiting or caring for someone with asthma. The direct cost of asthma for the UK National Health Service is estimated to be £1 billion per year with a

loss of around 1.1 million working days accounting for a large proportion of indirect costs (32). A study published in 2000 using UK audit data from general practice estimated the average cost for managing people with an asthma exacerbation was over 3.5 times higher than for people with stable asthma equating to an additional £273 per patient per year (33). Since then the cost of asthma care has increased significantly. In a population-based cohort study assessing trends in direct costs for asthma (2002 to 2007) in the province of British Columbia, Canada (population 4.5 million), direct costs for asthma were C\$315.9 million with hospitalisations, doctor visits and medication costs accounting for 16.0%, 15.7% and 68.2% respectively (34). During this time, direct cost related to asthma increased by C\$5.3 million (a 10.7% increase) mainly due to increased medicine costs and a rising prevalence of disease. A subsequent systematic review investigating the clinical, economic, and humanistic burden of asthma in Canada reported an average direct cost per patient with asthma of between C\$366 and C\$647 associated with high rates of psychological impact and reduced quality of life compared to people without asthma (35). In contrast, a 2011 study on the cost of asthma in the US reported an incremental direct cost of asthma of \$3259 per patient per year with an average indirect cost associated of \$301 per patient per year. The total incremental cost associated with asthma in the US for the years 2002 to 2007 was approximately \$56 billion (36). In this regard, asthma management remains a priority for many healthcare systems worldwide.

1.7.3 Severe asthma exacerbations and asthma death

Asthma is a chronic condition with episodes of acute exacerbations which may lead to hospitalisation and death. In 2010 in the US there were 14.2 million ambulatory care attendances for asthma and 1.8 million emergency department visits resulting in

439,000 hospitalisations, with an average length of stay of 3.6 days (31). Between 1981 and 1997 asthma hospital admission rates in Scotland increased from 106.7 to 236.7 per 100,000 population, a rise of 122%, (37). Similar increases in hospital attendances for severe asthma have been reported elsewhere, whilst in the US emergency department visits and hospitalisations have been stable (38, 39). Currently there are approximately 8,000 hospital attendances with asthma per year in Scotland with some evidence that hospital attendances are falling (40). Although hospitalisation is a proxy for severe asthma morbidity, A&E attendance or primary care management of an acute asthma exacerbation are both good measures of significant uncontrolled asthma morbidity.

Mortality rates for asthma vary globally being highest in China and Russia (36.7 and 28.6 per 100,000 persons with asthma respectively, for patients aged 5-34 years) (24). Comparable mortality rates for English speaking countries such as the US and Scotland during this period were 5.2 and 3.0 per 100,000 persons respectively despite having a higher prevalence of asthma. In the US, in-hospital mortality from asthma was estimated at 0.5% compared to 0.9% in Scotland (41, 42). However, this US study used data from 2000 to 2010 whilst the Scottish study used data from 1981 to 2009 and also included deaths soon after discharge. Other studies have reported lower in-hospital mortality rates for asthma both in the UK (0.43%) and Australia (0.14%) (43, 44). This heterogeneity in mortality could be explained by differences in healthcare provision but may also be related to the using different observation periods at a time when mortality rates for asthma have been falling (39, 42, 45). The US national vital statistics report for 2010 reported an asthma mortality rate of 1.1 per 100,000 person years (pyrs) which was comparable to Scotland for the same period (31).

1.7.4 Risk factors for severe asthma exacerbations and asthma death

Gender

Although women appear to be at increased risk of asthma hospitalisation, there are inconsistent reports of gender influencing in-hospital mortality. A prospective cohort study involving 64 emergency departments in North America found that the risk of asthma hospitalisation was twice as great in women than men (46). In another study involving 59,983 admissions from Taiwan women had increased duration of inpatient stay and cost associated with asthma (47). In contrast, one study found that men had a 39% increased risk of in-hospital mortality, a finding which has been noted by others (41, 47). Other studies have either reported an increased risk of asthma death in women or that gender is a non-significant predictor of in-hospital mortality (39, 42).

Age

There is an association between increasing age and increased risk of death from asthma. In a UK study investigating factors associated with the 30 day case fatality following hospitalisation for asthma, risk of death from asthma increased incrementally with age and was greatest in patients over the age of 65 (OR 12.3) (42), an association which has been reported elsewhere (39, 41, 47). In addition, there is also an association between increasing age and poor asthma control in general practice (48).

Smoking

Smoking is associated with poor asthma control and reduced response to ICS. In a study evaluating asthma morbidity in 950 patients from general practice, patients who smoked were half as likely to have good asthma control as non-smokers (48). Among 85 pregnant women with asthma, the number of asthma exacerbations was significantly

increased among current smokers than those who never smoked (52% and 35% respectively) (49). Following multivariate analysis, ACQ6 scores (a validated asthma control questionnaire for assessing the severity of waking at night, morning symptoms, limited activity, breathlessness, wheeze, beta2-agonist use and lung function consistent with asthma morbidity) were significantly elevated in current smokers compared to never smokers. Maternal smoking is also an independent predictor of hospitalisation for asthma in children (10). Also, smoking cessation can improve airway hyper-responsiveness and ACQ6 scores and introduction of smoke free legislation in the UK was associated with an immediate 4.9% fall in emergency admissions for asthma resulting in the prevention of an estimated 1900 emergency admissions for asthma 3 years following its introduction (50, 51).

Obesity

In a community-based adult asthma cohort, obesity was associated with increased asthma morbidity in terms of asthma-specific quality of life scores and an increase in health service use measured by emergency department and urgent care visits (52). Additionally, pregnant women with asthma and higher BMI have more severe exacerbations during pregnancy (49). In a prospective study involving 85,911 people aged 26 to 46 followed up for 4 years, patients with higher BMI were at a significantly increased risk of developing asthma (relative risk 2.7 for patients with BMI over 30 compared to patients in the normal range) (53). In contrast, weight reduction in obese asthma patients may improve lung function, reduce symptoms, and reduce rescue medication use and exacerbations (54).

Comorbidity

Several studies have demonstrated an increased risk of asthma hospitalization and death in people with comorbidities. In a retrospective case study from Scotland risk of asthma death was significantly increased in people with cancer, coronary heart disease, respiratory infection and renal failure (adjusted odds ratios 1.6-2.6) (42). In a large US study involving 65,381 asthma hospitalisations, mortality was significantly associated with increasing comorbidity as assessed by the Charlson comorbidity index (a validated score which predicts the ten-year mortality for people with a range of comorbid conditions) (41). Other studies have shown an increased risk in asthma death following hospitalisation in people with co-existing respiratory disease, cardiovascular disease, endocrine disease, genitourinary disease and cancer (47).

Other risk factors

Other risk factors for poor asthma control, hospitalisation and death from asthma exist. Patients treated with oral steroids for asthma, people receiving nebulised asthma medication and people receiving asthma medication other than beta-agonists and ICS appear to have a significantly increased risk of asthma hospitalisation (46). Other factors such as medication adherence and objective measurements related to the severity of an exacerbation at the time of presentation (e.g. respiratory rate and PEF) are important in predicting risk of asthma hospitalisation and death.

An important case-series analysis of 283 cases of asthma deaths in people under the age of 70 from Australia found that 60% of asthma deaths actually occurred at home. Among the case series, 65% of patients were from deprived socioeconomic areas with only 37% of deceased patients in employment (55). In addition, psychosocial factors

such as co-existing mental health illnesses were present in just under half of fatalities. Drug and alcohol use was found to be an important factor in 34% of fatalities whilst inadequate treatment (self-management and the provision of asthma care) was a factor in 18%. Other potential risk factors for asthma death included living rurally and delay in seeking help. Of the people who died, 46% suffered sudden onset asthma exacerbations not preceded by a gradual deterioration in symptom control. Other triggers included food, beta-blockers, non-steroidal anti-inflammatory drugs (NSAIDs) and exposure to smoke and fumes (55). In total around 70% of fatalities were considered potentially preventable. The National Review of Asthma Deaths is a similar case series analysis led by the Royal College of Physicians in the UK to better understand the circumstances surrounding asthma deaths which occurred between February 2012 and January 2013. This review found that 45% of asthma deaths occurred in people not seeking medical attention and that around half of patients had a previous history of hospital admission (56). In addition, 43% of people who died of asthma did not attend a primary care based asthma review in the year before death. Overall it was felt that 46% of asthma deaths could have been prevented.

In summary, asthma is a common problem globally. It affects people of all ages, causes a high degree of morbidity and is associated with a high economic burden. This highlights the importance of properly quantifying the risk factors for asthma exacerbations which affect large numbers of patients and may be preventable. This knowledge will help understand the methods and results used in subsequent chapters.

1.8 Pharmacological management of asthma

The aim of asthma management is to achieve complete asthma control defined as the absence of all of daytime symptoms, night-time waking, need for rescue therapy, acute exacerbations and restrictions to daily living, whilst normalising lung function and minimising side effects of therapy (2). There is a stepwise approach to the pharmacological management of asthma whereby patients commence at the step most appropriate to the severity of their symptoms. Control is then achieved and maintained through the addition or withdrawal of medications in a stepwise fashion following checks of adherence and inhaler technique. In this regard, the number of asthma medications or the management step a patient is at can be an important marker of asthma severity.

The first step for mild intermittent asthma is to use an inhaled short-acting beta2-agonist (SABA) which causes temporary bronchodilation and provides short-term relief of asthma symptoms. As SABAs do not treat the underlying cause of asthma (airway inflammation) they are often referred to as relievers. However, frequent need for reliever therapy (using more than 2 canisters of SABA per month) is a marker of poor asthma control and a risk factor for asthma death and should prompt medical review (57). Medications which alter the underlying airway inflammatory process are often referred to as preventers. Regular preventer therapy with an ICS is used at step 2 of the guidance. Different types of ICS exist with beclometasone and budesonide having equivalent clinical doses whilst fluticasone, mometasone and ciclesonide are approximately equivalent at half the dose (2). When used appropriately, ICS are considered the most effective anti-inflammatory therapy to achieve full asthma control and should be considered in patients with persistent asthma using SABA three or more

times per week, and/or with symptoms causing night-time wakening, or in those who have received oral steroids for asthma in the last two years. In a Cochrane systematic review evaluating inhaled beclometasone versus placebo for chronic asthma involving 6542 patients, 400mcg per day of inhaled beclometasone over four weeks in steroid naïve patients lead to improved lung function (improvements in FEV1 of 360ml and in PEFR of 36 L/min), reduction in the use of SABA therapy (-2.3 puffs/day) and reduction in the risk of an asthma exacerbation (relative risk 0.25, 95%CI 0.12 to 0.51). In people treated with maintenance oral steroids, inhaled beclometasone lead to a greater reduction in daily oral steroid use and increased the chance of oral steroid withdrawal (IRR 8.02, 95% CI 3.23 to 19.92) (58). Regular use of ICS in asthma is also associated with a reduced risk of death (59). However, ICS only help to control airway inflammation and symptoms may recur following discontinuation (60).

ICS therapy is generally considered safe although common side effects include dysphonia and oropharyngeal candidiasis. Adrenal suppression is a rare side effect in children on high doses of ICS. In contrast there is no consensus that ICS significantly alter bone mineral density leading to an increased fracture risk, although this is well recognised with the use of systemic corticosteroids (61-63). One meta-analysis of case-control studies demonstrated that in older adults, the relative risk of non-vertebral fractures increased by approximately 12% for each 1000mcg/day increase in beclometasone equivalent dose and was far less than other common risk factors for fractures (64).

Step 3 consists of initial add-on therapy with either a long-acting beta2-agonist (LABA; generally recommended as first choice) or a leukotriene receptor antagonist. LABAs

improve lung function and quality of life however, chronic LABA exposure may cause tolerance to the effects of beta-agonists raising concerns over their use in asthma (65). The SMART (Salmeterol Multi-Centre Asthma Research Trial) randomised controlled trial involved 26355 patients randomised to a LABA (salmeterol) or placebo in addition to their usual care, and reported an increase in asthma-related deaths in LABA-treated patients (IRR 4.37, 95% CI 1.3 to 15.3) (66). This risk was potentially confined to patients using LABA monotherapy only, which is why LABAs are only recommended for the management of asthma in combination with ICS. Leukotriene receptor antagonists inhibit the production of cysteinyl leukotrienes (potent bronchoconstrictors in asthma) and can improve lung function, airway inflammation and reduce exacerbations (1). In contrast to LABAs, leukotriene antagonists are generally recommended as the second choice add-on therapy although results from a pragmatic clinical trial suggest that either add-on therapy is equally effective (67). Step 4 consists of adding a fourth drug such as oral theophylline which acts as a bronchodilator but commonly causes adverse effects due to its narrow therapeutic window. Step 5 is the frequent or continuous use of oral steroids. This stepwise approach can be managed in primary and secondary care. Other therapies available for poorly controlled patients with asthma include omalizumab (an anti-IgE monoclonal antibody reserved for poorly controlled atopic patients) but are typically only administered in secondary care.

In summary, there is a stepwise approach to the pharmacological management of asthma based on a patient's underlying severity of symptoms. This highlights the importance of establishing severity and/or current patterns of asthma medication use when attempting to quantify the risk of triggers such as beta-blockers and NSAIDs in asthma.

1.9 Beta-blockers and asthma

1.9.1 Beta-adrenoceptors

The actions of endogenous and exogenous circulating catecholamines are mediated through alpha- and beta-adrenergic receptors present on cell membranes in different tissue types in the body including blood vessels, heart and lungs. Beta-adrenoceptors are located on the walls of blood vessels and vascular smooth muscle cells, where they cause vasodilation in response to catecholamine stimulation. Although beta-1 and beta-2 adrenoceptors have been detected in blood vessels, their distribution appears to differ according to the type of blood vessel. Beta-1 adrenoceptors appear to have a dominant role in mediating vasodilation whilst beta-2 adrenoceptors mediate vasodilation in major blood vessels only such as the aorta, carotid arteries and portal vein (68). The heart contains beta-1, beta-2 and beta-3 adrenoceptors. Stimulation of myocardial beta-1 and beta-2 adrenoceptors results in positive inotropy (increased force of contraction) and chronotropy (increase heart rate). In contrast, beta-3 adrenoceptors tend to inhibit inotropy when stimulated. The beta2-adrenoceptor is the predominant pulmonary adrenoceptor subtype responsible for airway smooth muscle relaxation and bronchodilation, although small numbers of beta-1 and beta-3 subtypes have been detected in human bronchial epithelial cells as well (69).

1.9.2 Beta-blockers

Beta-blockers first came into clinical use in the 1960s after Sir James Black demonstrated that the non-selective beta-blocker propranolol lowered myocardial oxygen demand by inhibiting the effects of catecholamines, an observation which led to major clinical advances in the management of several cardiovascular diseases (70).

However, it soon became apparent that non-selective beta-blockers may cause adverse respiratory effects in people with asthma. In an attempt to avoid adverse effects novel beta-blockers were manufactured with greater subtype selectivity for the beta-1 adrenoceptor, including those with partial agonist and alpha-adrenergic activity. The first selective beta-blocker in clinical use was practolol, but was withdrawn from the market because it caused retroperitoneal fibrosis (71).

Although beta-blockers are now classified as either selective or non-selective, significant differences in their relative affinities to the beta-1 and beta-2 adrenoceptor exist. Among non-selective beta-blockers, timolol has the highest affinity for the beta-2 adrenoceptor (25.7-fold beta-2 selective) followed by nadolol (23.4-fold), sotalol (12.0-fold), propranolol (8.3-fold), carvedilol (4.5-fold) and labetalol (2.5-fold) (72). Among selective beta-blockers, bisoprolol has the highest affinity for the beta-1 adrenoceptor (13.5-fold more beta-1 selective) followed by betaxolol (6.8-fold), atenolol (4.3-fold), acebutolol (2.4-fold) and metoprolol (2.3-fold). Some beta-blockers are described as having intrinsic sympathomimetic activity (partial agonist activity) which occurs when antagonist binding causes some stimulation of the receptor. However it is generally regarded that beta-blocker ISA does not confer any particular clinical advantage.

1.9.3 Clinical indications for beta-blockers

Beta-blockers are recommended first line drugs for the relief of angina. In a meta-analysis of clinical trials comparing beta-blockers to calcium channel antagonists and nitrates, beta-blockers were better at preventing episodes of angina and were better tolerated than other agents (although no difference in cardiovascular mortality was found) (73). Beta-blockers have been shown to reduce mortality following myocardial

infarction (74). Although beta-blockers are licenced for the treatment of hypertension, they are not currently recommended as first line agents because they are considered less effective than diuretics, calcium channel blockers and renin angiotensin system inhibitors (75). Beta-blockers are also used in the treatment of anxiety and migraine. In a meta-analysis of 58 trials involving 5072 patients, propranolol was associated with clear short term benefits in migraine prophylaxis over placebo (76). Topical beta-blocker eye drops such as timolol and betaxolol are commonly used in the treatment of ocular hypertension and can prevent visual field loss in glaucoma (OR 0.7 (95%CI 0.5-1.0)) (77). However, despite being applied locally, systemic absorption and adverse effects may occur.

Beta-blockers are indicated in the treatment of heart failure. In heart failure, reduced peripheral oxygen levels stimulate an excess release of endogenous catecholamines leading to short-term improvements in myocardial contractility. In this regard, beta-agonists such as dobutamine were once routinely used in the treatment of heart failure but were subsequently found to increase mortality (78). Chronic exposure to several beta-blockers including bisoprolol, metoprolol and carvedilol has been proven to significantly reduce mortality by around 30% and hospitalisations in patients with left ventricular systolic dysfunction (79). Although acute beta-blocker exposure in heart failure may cause transient reductions in myocardial contractility, beta-blockers are often well tolerated if initiated at a low dose with gradual dose escalation (80).

1.9.4 Beta-blockers in asthma

Soon after their introduction it became apparent that beta-blockers triggered exacerbations in susceptible people with asthma. In a study published in 1966 in the

Lancet, intravenous propranolol caused marked reductions in FEV1 and symptoms in 4 of 10 patients with asthma (81). This adverse respiratory effect is caused by antagonism of endogenous catecholamines at the pulmonary beta2-adrenoceptor leading to unopposed cholinergic tone.

As a result of these adverse respiratory effects in susceptible people, it was recommended that all beta-blockers should be contraindicated in people with asthma; recommendations which continue to appear in current asthma guidelines (1, 2). Asthma deaths associated with beta-blocker exposure (including topical agents) have been reported, often in people with uncontrolled asthma or in those receiving high doses of acute non-selective beta-blocker therapy (55, 82, 83). Despite these safety concerns, beta-blockers are still prescribed to patients with asthma. In a cross-sectional study which I carried out before starting the PhD, beta-blockers were prescribed to 2.2% of adult patients with asthma over the course of a year, many of whom received repeat prescriptions (84). On the one hand, this observation may suggest inappropriate prescribing but equally there may be strong clinical indications for using beta-blockers in some people. From this perspective, beta-blockers are also often withheld in people with asthma who also have strong cardiovascular indications. In a study investigating the current use of beta-blockers in patients hospitalised with acute coronary syndrome, patients with reversible airways disease were 42% less likely to be prescribed a beta-blocker (85, 86), probably because the risk was assumed to outweigh the benefits. However, the adverse respiratory effect of beta-blockers in asthma has been poorly quantified.

In reality, most beta-blockers used in cardiovascular disease are subtype selective and may not have the same risk because they preferentially antagonise the beta1-adrenoceptor more than the beta2-adrenoceptor. The adverse respiratory effect of selective beta-blockers in patients with reversible airways disease (asthma and COPD) has previously been systematically evaluated. This meta-analysis of 19 clinical trials evaluating single dose selective beta-blocker exposure reported only small mean falls in FEV1 of 7.46% with no significant increase in symptoms among patients from included studies (87). However, this analysis is potentially limited as the effects of selective beta-blockers may vary by dose and by individual susceptibility in which case use of mean values alone may mask a clinically significant risk in a proportion of people. In contrast, the adverse respiratory effect of non-selective beta-blocker exposure in asthma has not been systematically evaluated even though a small proportion of patients with asthma are prescribed non-selective agents periodically. Additionally, beta2-agonists are first-line rescue therapy for acute bronchoconstriction and in theory their efficacy could be reduced in patients taking beta-blockers. Chapter 3 reports a systematic review and meta-analysis of the fairly numerous small clinical trials evaluating the effect of beta-blocker exposure in patients with asthma, including evaluating the proportion with a clinically significant reduction in FEV1, and the effects of non-selective beta-blockers.

The effect of beta-blocker exposure in asthma still remains largely uncertain. In this regard, two observational studies have attempted to evaluate the risk of hospitalisation in patients with either asthma or COPD exposed to beta-blockers. In a retrospective cohort study by Brooks et al., selective beta-blockers were associated with a significantly increased risk of emergency department visits (relative risk 1.47) whilst non-selective beta-blockers were associated with a significantly increased risk of

hospitalisation (relative risk 2.47) (88). However, this analysis did not adjust for potential confounders. In contrast, a similar study involving patients with asthma and COPD also demonstrated significantly higher rates for hospitalisation in patients taking selective (11.6%) and non-selective (9.4%) beta-blockers compared to controls (8.3%). Following adjustment however, the risk for hospitalisation in both classes of beta-blocker was not significantly different to controls (OR 1.16, 95%CI 0.98-1.35 and 1.11, 95%CI 0.73-1.69 respectively) suggesting that underlying confounding may have explained the increased risk with the analysis in the previous study (89). Chapters 7 and 8 report a nested case control study evaluating the effect of beta-blocker exposure in patients with asthma, including evaluating risk associated with incident and prevalent exposure.

In summary, beta-blockers antagonise the effects of catecholamines at beta-adrenoceptors. Several beta-adrenoceptor subtypes exist which are differentially distributed throughout the body. Different beta-blockers exhibit different degrees of beta-adrenoceptor subtype selectivity and their effects in asthma may differ according to acute or chronic exposure. The adverse respiratory effect of beta-blockers is traditionally thought to affect all people with asthma equally but individual susceptibility may occur. Risk of beta-blockade in asthma has not been well quantified despite the strong warnings against their use in asthma, which is important for people where beta-blockers would have major benefit.

1.10 Non-steroidal anti-inflammatory drugs and asthma

1.10.1 Mechanism of action of aspirin and NSAIDs

Aspirin and other NSAIDs are effective anti-inflammatory, analgesic and antipyretic agents which irreversibly inhibit cyclooxygenase enzymes (COX) and reduce prostaglandin synthesis from their precursor arachidonic acid. Two isoforms of COX exist. COX-1 is constitutively expressed in most tissues whilst COX-2 is induced by inflammatory stimuli such as cytokines (90). Inhibition of COX-2 is thought to account for the therapeutic effects of aspirin and other NSAIDs whilst inhibition of COX-1 is thought to account for many of their side effects. This prompted the development of newer more selective NSAIDs specifically targeting COX-2. In a similar fashion to beta-blockers, aspirin and other NSAIDs have been classified as having differing COX-2 selectivity which varies by agent. In an in vitro analysis, aspirin, ibuprofen, naproxen, indomethacin, ketorolac, diclofenac, piroxicam and sulindac fully inhibited COX-1 and COX-2 and were considered to have relatively poor selectivity. In contrast, meloxicam and nimesulide showed preferential COX-2 selectivity (>5 fold) whilst the COX-2 inhibitors generally had the greatest degree of preferential COX-2 selectivity (>50 fold) (91).

1.10.2 Clinical indications for NSAIDs

NSAIDs are recommended in guidelines for the chronic management of musculoskeletal conditions and for the short-term management of pain and febrile illnesses (92). In contrast aspirin is primarily used in the secondary prevention of cardiovascular conditions due to its antiplatelet effects. Aspirin and NSAIDs are commonly prescribed. In 2010 in the US, an estimated 43 million adults took aspirin

(defined as three or more times per week for 3 months) and a further 29 million adult took NSAIDs, an increase of 57% and 41% respectively since 2005 (93).

1.10.3 Aspirin-exacerbated respiratory disease

In susceptible people with asthma, COX-1 inhibition by aspirin alters the balance between proinflammatory and anti-inflammatory mediators, leading to increased levels of cysteinyl leukotrienes (LT) and bronchoconstriction (94, 95). Arachidonic acid is usually converted to leukotriene A₄ (LTA₄) by the enzyme 5-lipoxygenase (5-LO). LTA₄ is then subsequently converted to LTC₄ by the action of LTC₄ synthase enzyme which is often overexpressed in susceptible patients. Cysteinyl leukotrienes then bind to specific G-protein transmembrane receptors in the airway (CysLT₁ and 2) causing bronchoconstriction (90). By inhibiting the COX pathway in susceptible individuals, aspirin diverts more arachadonic acid through the lipoxygenase pathway thus increasing leukotriene production whilst at the same time reducing the synthesis of prostaglandin E₂ (PGE₂). PGE₂ helps to regulate the inflammatory system by inhibiting 5-LO, cholinergic tone and the release of mediators from mast cells (96).

Although initially described with aspirin, cross-reactivity with other nonselective NSAIDs is thought to occur in the majority of patients with this phenotype, usually referred to as aspirin-exacerbated respiratory disease (AERD) (97). Patients with the AERD phenotype are more likely to have chronic rhinosinusitis and nasal polyposis and aspirin can also trigger upper respiratory symptoms such as rhinorrhoea and nasal obstruction. Few large scale observational studies investigating AERD have been performed. One European-wide survey involving ten European centres and 500 participants with AERD demonstrated that AERD often developed according to a

sequence of events commencing with rhinitis followed by asthma, aspirin-intolerance and lastly nasal polyposis starting around the age of 30 years (98).

However, the prevalence of AERD is inconsistently reported in the literature, varying between 4% and 44%, mainly as a result of heterogeneity in AERD definition, patient selection and study design. For example, McDonald et al. pre-selected asthma patients with nasal polyps or severe asthma, exposed them to 320mg of aspirin and determined AERD by a fall in FEV1 of $\geq 50\%$ (99). In contrast, other investigators have used unselected patients, lower doses of aspirin and lower values of FEV1 to define aspirin sensitivity. Most studies attempting to establish the prevalence of AERD have either used self-reported patient questionnaires or oral challenge tests. One previous systematic review attempting to estimate the prevalence of AERD reported a figure of 21% for adults and 5% for children with asthma suggesting that AERD is perhaps more prevalent than previously thought (97). However this systematic review included several unblinded and uncontrolled provocation challenge tests aimed at detecting AERD which could be subject to bias or placebo-effect. Chapter 4 reports a systematic review and meta-analysis of small clinical trials and population based surveys measuring the prevalence of AERD in patients with asthma.

In patients with AERD, risk from NSAIDs is considered greatest after acute exposure, with reactions typically occurring within 3 hours of ingestion. These reactions can be severe, with case reports of serious adverse events and fatalities as a result of NSAID exposure (100). Guidelines for the management of asthma currently recommend asking people about past reactions before prescribing an NSAID or advise avoiding NSAIDs altogether (2, 101). This in itself can be problematic because self-awareness of

NSAID-induced symptoms in people with asthma is not universal (98). As such, these recommendations have important clinical implications for the use of NSAIDs, to the extent that NSAIDs are often either withheld or prescribed with uncertain clinical consequences. In one large observational study, between 15.7% and 21.5% of asthmatics had an NSAID prescription in the last 12 months (102). Additionally, patients might be unwilling to accept the risk associated with first (incident) exposure or conversely might risk exposure from over-the-counter medications without appropriate medical supervision.

In people with suspected AERD, all NSAIDs are contraindicated by the US Food and Drug Administration, with no comment regarding risk from the newer selective agents (103). This contraindication is mirrored in the United Kingdom by the Medicines and Healthcare Products Regulatory Agency–approved Summary of Product Characteristics for COX-2 inhibitors, which clearly states that COX-2 inhibitors should not be taken if patients have a history of asthma symptoms after taking aspirin or any other NSAID (104). Selective NSAIDs, such as meloxicam, and COX-2 inhibitors, such as celecoxib, act through preferential inhibition of COX-2 over COX-1, leaving the balance between proinflammatory and anti-inflammatory mediators unaltered and cysteinyl leukotriene levels unchanged (105). Therefore selective NSAIDs, COX-2 inhibitors, or both would be expected to have a lower risk of adverse respiratory effects in patients with AERD. Several clinical trials evaluating the effect of selective NSAID and COX-2 inhibitor exposure in patients with AERD have been conducted, and chapter 5 reports a systematic review and meta-analysis of these trials. In summary, aspirin and other NSAIDs are widely used medications that can cause bronchoconstriction in susceptible people with asthma. In a similar fashion to beta-blockers, NSAIDs also exhibit differing

degrees of selectivity to COX enzymes and their effects in people with asthma may differ according to their degree of selectivity. Uncertainty regarding the prevalence of AERD still remains which is a problem in appreciating risk from aspirin and NSAIDs at a population level.

1.11 Summary

Asthma is a common complex condition often associated with comorbidity and high health care utilisation. Beta-blockers and NSAIDs are widely prescribed medicines that have long been known to trigger exacerbations in susceptible people with asthma. It is now becoming established that asthma is a heterogeneous condition associated with different phenotypes like AERD. The adverse respiratory effect of beta-blockers leading to unopposed cholinergic tone is traditionally thought to affect all people with asthma. However, it could be that some people with asthma may tolerate beta-blockers well.

Guideline recommendations typically rely on a historic evidence base conducted at a time when use of ICS and other asthma medications were not widespread. These recommendations have led to the avoidance of beta-blockers and NSAIDs in some people who may benefit from their use or conversely may be prescribed inappropriately leading to adverse respiratory events. The effectiveness of these agents in the management of cardiovascular disease and pain has been well established. In contrast, risk from beta-blockers and NSAIDs in asthma has been relatively poorly quantified making it difficult for clinicians to be certain if the risks outweigh potential benefits. Evidence to quantify adverse effects of drugs can come from controlled clinical trials and observational studies. Controlled clinical trials establish causality and are considered to provide evidence that has strong internal validity but results may not be

generalizable due to the highly selected people eligible to participate. In contrast, observational studies can provide evidence with strong external validity and are good at detecting uncommon adverse drug events. However, causation may be more difficult to establish with observational studies which can suffer from residual confounding. In this regard, using both types of evidence should provide robust evidence to quantify the risk of these agents in people with asthma.

1.12 Study aims

The aim of this thesis is to quantify the risk of beta-blocker and NSAID exposure in people with asthma by systematically synthesising clinical trial evidence and conducting new observational studies using routine linked electronic health care records.

1.13 Research questions

The research questions designed to meet the above aims of the thesis include:

1. Among people with asthma, what is the prevalence of beta-blocker and NSAID prescribing?
2. How frequently do beta-blockers and NSAIDs trigger changes in lung function and respiratory symptoms in people with asthma?
3. Do the frequency and severity of reactions vary among different classes of beta-blockers and NSAIDs?

The next chapter will provide a detailed outline of the general methods used in a variety of analyses in this thesis.

Chapter 2: General Methods

2.1 Introduction

This chapter provides background to the different methods used in this thesis. In the first phase, existing evidence from clinical trials was synthesized to quantify how frequently beta-blockers and NSAIDs trigger changes in lung function and respiratory symptoms in people with asthma. This was conducted using the principles of systematic review and meta-analysis set out in this chapter. Following this, the population at risk from beta-blocker and NSAID exposure was defined using routine electronic health care records from the Clinical Practice Research Datalink (CPRD) and the prevalence of beta-blocker and NSAID prescribing for a twelve year period in the UK measured. Lastly, several nested case control and self-controlled case series studies using data from CPRD were conducted to estimate the frequency and severity of adverse respiratory events associated with beta-blocker and NSAID exposure with a particular emphasis on whether risk varied by class, duration of administration and dose where appropriate.

2.2 Systematic reviews and meta-analyses

This section presents details of the methods for systematic reviewing and meta-analysis which are common to the three systematic reviews in this thesis. Specific methods or issues unique to each systematic review and meta-analysis are described in the relevant chapter.

2.2.1 Systematic review search strategies

Systematic searches of MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were performed to identify all clinical trials published on or before April 2013 which evaluated acute exposure to the drug of

interest. In this regard, pre-specified search strategies were used and focused upon three main concepts namely; ‘asthma’, ‘clinical trials’ and ‘the drug of interest’. The exception to this was for the systematic review on the prevalence of aspirin-exacerbated respiratory disease (AERD) which additionally evaluated the prevalence of AERD using population studies using self-reported history (chapter 4). The detailed search strategies for OvidSP MEDLINE for each systematic review are shown in appendix 1. A meta-analysis of observational studies evaluating risk of exposure was not performed because the number of studies identified on scoping was small and meta-analysis would have been methodologically more complex.

2.2.2 Systematic review selection criteria

For each systematic review conducted, pre-specified selection criteria were established to select published studies for inclusion. These selection criteria followed a standard PICOS approach which consisted of the following:

P = defining the population of interest including inclusion and exclusion criteria

I = defining the intervention of interest namely acute exposure to the drug of interest

C = defining the comparator namely placebo

O = defining the outcomes of interest namely changes in lung function and symptoms

S = defining the study designs to be included within each systematic review

2.2.3 Systematic review data processing and extraction

For each systematic review, all identified references were compiled into an Endnote database. Identified references were then independently screened by me and a second reviewer. References clearly not meeting the eligibility criteria were rejected, with ambiguous titles/abstracts retained for full text review. Full texts were then

independently appraised by the two reviewers. At each stage the decision to include articles was based upon consensus between reviewers. Manual searches from the reference lists of included studies were performed to identify additional articles. Only English language publications were included in the systematic. Only published data from eligible studies were extracted and used in the systematic review and meta-analyses. This was a pragmatic decision based upon the resources and time available. A standardised data extraction form was used to extract data from included studies.

2.2.4 Systematic review data analysis

For each systematic review and meta-analysis, extracted data from included studies were entered into an SPSS v21 database. Outcomes of interest included:

- Mean percentage change in forced expiratory volume in one second (FEV1)
- Falls in FEV1 of 20% or greater in order to better assess individual susceptibility
- Incidence of respiratory symptoms to better distinguish between symptomatic and asymptomatic changes in lung function

These outcomes were calculated for both placebo and the exposure of interest. All measures of FEV1 were calculated relative to original baseline FEV1 values. For meta-analyses which included the mean percentage change in FEV1 (continuous outcome) as an outcome (specifically the beta-blocker meta-analyses, chapters 3) results are presented as the mean difference. The mean difference measures the absolute difference in mean percentage change between two groups when values are measured using the same scale (in this case FEV1). Falls in FEV1 of 20% or greater and the incidence of patient-recognised respiratory symptoms were defined as outcomes to better assess individual response. For example, some people with asthma may be extremely sensitive

to the effects of beta-blockers because they heavily rely upon sympathetic drive to maintain airway smooth muscle tone and risk in these individuals may not be fully appreciated with group means. For falls in FEV1 of 20% or greater and the incidence of respiratory symptoms (dichotomous outcomes), outcome measures were defined in terms of the risk difference (RD). The risk difference is the difference in observed risk between two groups and provides a measure of absolute effect. The risk difference was used because it is an absolute measure which allows the numbers needed to harm to be calculated by dividing 1 by the risk difference. Another advantage of the risk difference compared to the risk ratio is that it can be estimated between groups with no events so that these studies may still be included in the meta-analysis.

Mantel-Haenszel summary risk difference for dichotomous outcomes

Meta-analysis was performed in Review Manager (RevMan) version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). A Mantel-Haenszel method of analysis was used to calculate the risk difference for dichotomous outcomes (equation 1). The Mantel-Haenszel method is typically used when events are few or sample sizes are small as with many of the included studies. For dichotomous outcomes where there are few events or small sample sizes, the Mantel-Haenszel method is considered to perform better than other methods such as the inverse variance method. The Mantel-Haenszel summary risk difference (RD_{MH}) was calculated as the weighted sum of the risk differences for the i individual studies (RD_i) (106):

$$RD_{MH} = \frac{\sum w_{MH,i} RD_i}{\sum w_{MH,i}}$$

Equation 1. Mantel-Haenszel summary risk difference.

Each study's risk difference is given weight ($w_{MH,i}$) as follows, where (i) is the study, n_{1i} is the number of participants in the experimental group and n_{2i} is the number of participants in the placebo group for study i , and N_i is the total number of participants in study i :

$$w_{MH,i} = \frac{n_{1i}n_{2i}}{N_i}$$

Equation 2. Weighting the risk difference for each study.

The summary risk difference has a standard error (SE) of:

$$SE\{RD_{MH}\} = \sqrt{\frac{J}{K^2}},$$

Equation 3. Standard error for the Mantel-Haenszel summary risk difference.

Where a_i and c_i are the number of events in the treatment and control groups respectively, and b_i and d_i are the number with no event in the experimental and control groups respectively, and J and K are given by:

$$J = \sum \frac{a_i b_i n_{2i}^3 + c_i d_i n_{1i}^3}{n_{1i} n_{2i} N_i^2}; \quad K = \sum \frac{n_{1i} n_{2i}}{N_i}.$$

Where a , b and n represent the sample size for each respective group as shown in table 1.

Table 1. Reference groups used to calculate the Mantel-Haenszel summary risk difference

Binary data Study i	Event	No event	Total
Experimental	a_i	b_i	n_{1i}
Control	c_i	d_i	n_{2i}

Generic inverse-variance for mean difference, mean provocative dose

Inverse-variance weighting is an approach whereby the weight given to each study is the inverse of the variance of the effect estimate (107). In this regard, larger studies which have smaller standard errors are given more weight than smaller studies with larger standard errors. The following approach was used in estimating the summary effect estimates using the mean difference (chapter 3) and the mean provocative dose (chapter 4). The study effect estimates were calculated using inverse-variance weighting to pool effect estimates from studies in which the standard deviation could be derived. Standard deviations were then converted to standard errors (SE) using the following formula, where N is the sample size (108):

$$SE = \frac{SD}{\sqrt{N}}$$

Equation 4. Calculating the standard error from the standard deviation.

The fixed-effect inverse-variance weighted mean (ES) was then calculated as follows where X_i is the group mean for study i and SE_i is the standard error for the group:

$$ES = \frac{\sum X_i (1/SE_i^2)}{\sum (1/SE_i^2)}$$

Equation 5. Calculating the inverse-variance weighted mean

The standard error of the inverse-variance weighted mean (ES) was then calculated as follows:

$$SE_{ES} = \sqrt{\frac{1}{\sum (1/SE_i^2)}}$$

Equation 6. Calculating the standard error of the inverse-variance weighted mean

The 95% confidence interval of the inverse-variance weighted mean was calculated as follows:

$$Lower = ES - 1.96 (SE_{ES})$$

$$Upper = ES + 1.96 (SE_{ES})$$

Equation 7. Calculating 95% confidence intervals using the standard error

Firstly, studies reporting the mean difference between groups were identified and the mean difference extracted. When studies did not specifically report the mean difference, it was obtained by calculating the difference in means as follows:

$$MD = M_T - M_P$$

Equation 8. Calculating the mean difference

Where MD is the mean difference and M_T and M_P are the mean for the treatment and placebo measurements respectively.

Estimating the standard deviation from the range

For some included studies in the meta-analysis assessing the mean provocative dose (chapter 4) no other measure of variability or precision apart from the minimum and maximum threshold doses for the group (the range) were reported. In this instance, standard deviations were estimated from the range according to the method described by Hozo et al. (109). Briefly, this method states that for group sample sizes between 15 and 70, the standard deviation can be closely estimated by dividing the range by 4 assuming a normal distribution (where the range is the difference between maximum and minimum threshold dose for the group). For sample sizes greater than 70, range divided by 6 is suggested as the most appropriate estimator for the standard deviation. For

sample sizes less than 15, the variance can be estimated using the following formula providing the median (m) is known:

$$SD^2 \approx \frac{1}{12} \left\{ \frac{(a - 2m + b)^2}{4} + (b - a)^2 \right\}$$

Equation 9. Calculating the standard deviation using the range

Where a and b are the minimum and maximum threshold doses for the group.

Estimating the standard deviation for a continuous outcome using P -values

In order to meta-analyse continuous outcomes, data on the mean, standard deviation and sample size is required. Many of the studies identified and included in the systematic review and meta-analyses were cross-over trials reporting change from baseline values. Although baseline and post-intervention means may be reported with their respective standard deviations, it is not possible to calculate the standard deviation of the mean difference directly which is potentially problematic when performing meta-analysis (108). Several methods for dealing with this problem have been proposed which were applied to the beta-blocker meta-analysis reported in chapter 3.

Ideally, additional data would be requested from authors, but this was not done as the majority of studies were published 15 or more years ago reducing the likelihood of obtaining useful information. It was judged that there was insufficient time available to pursue this option for what would likely be a small return. Therefore, when standard deviations for the mean difference were missing, studies were first inspected to see if they reported individual patient data. Individual patient data were then extracted into a SPSSv21 database and used to calculate the standard deviation of the mean percentage difference using a paired t-test.

In the absence of individual patient data, standard deviations for mean differences may be calculated providing a standard error, confidence interval, *t*-value or *P*-value relating to the differences between the means of the two groups is provided (108). These calculations assume that the standard deviations associated with the outcome measurements are the same for both groups. In this setting the standard deviation is then used for both the treatment and placebo groups. The method for obtaining each value described in the meta-analyses is shown below. The standard deviation for the mean percentage difference was calculated using the *p*-value from a paired analysis through a three step process which involved calculating the *t*-score, the standard error and finally the standard deviation as follows (108):

1. Calculating the *t*-value from the *p*-value

Where *p*-values from a paired *t*-test were used to estimate the standard deviation, *t*-values were obtained by using the following formula in a Microsoft Excel spreadsheet:

$$t\text{-value} = \text{tinv}(p\text{-value}, df)$$

Equation 10. Calculating the *t*-value

tinv is a Microsoft Excel command which estimates the *t*-value of the Student's *t*-distribution as a function of the probability and the degrees of freedom and *df* are the degrees of freedom given by:

$$N_T + N_C - 2$$

Equation 11. Calculating the degrees of freedom for estimating the *t*-value

Where N_T and N_C are the sample sizes in the treatment and control groups respectively.

2. Calculating the standard error from the t-value

The t-value is the ratio of the mean difference to the standard error of the mean difference (108). Therefore, the standard error of the mean difference can be calculated by dividing the mean difference (MD) by the t-value:

$$SE = \frac{MD}{t}$$

Equation 12. Calculating the standard error of the mean difference

3. Calculating the standard deviation from the standard error

The missing standard deviation for mean percentage change was calculated from the standard error (SE) as follows:

$$SD = \frac{SE}{\sqrt{\frac{1}{N_T} + \frac{1}{N_C}}}$$

Equation 13. Calculating the standard deviation for the mean difference

Where N_E and N_C represent sample sizes for the treatment and control groups respectively. Using this approach, the standard deviation is used for both groups because it is the mean of the standard deviations of the treatment and control groups.

However, p-values for significant results were not always reported accurately, sometimes only being reported as being below particular threshold (e.g. $p < 0.05$). In this instance the standard deviation of the mean difference can still be estimated. In this instance, the standard approach is to round the p-value up and to use this to calculate a conservative estimate of standard deviation (110). Therefore, for a study reporting a significant analysis as $p < 0.05$, the standard deviation would be calculated as described above assuming $p = 0.05$. However, this approach was not used for p-values reported as

non-significant e.g. $p > 0.05$ since there is then no threshold to round up to. In this instance, studies which provided individual patient data were re-analysed and non-significant p-values pooled. The median non-significant p-value was then used to estimate the standard deviation. For the small number of standard deviations which could not be estimated using one of these methods, the median standard deviation of the group under investigation was imputed. Sensitivity analyses were performed to check the robustness of results using the minimum and maximum imputed p-value to ensure conclusions remained unchanged.

Statistical heterogeneity

Meta-analysis was used to statistically combine the results from separate studies, a process which relies on pooling the weighted average of the effect estimates between different studies in order to increase power and improve precision of the effect estimate. For each meta-analysis, a summary statistic was first produced for each study which was then pooled to generate a summary effect estimate which is weighted by the number of participants and the variance in each study. The variance between each study is referred to in meta-analysis as statistical heterogeneity which can result from clinical differences between participants, outcomes or methodological approach (107).

Heterogeneity among studies is important to assess in order to determine whether or not a fixed-effect or random-effects method of analysis was chosen. Other forms of non-statistical heterogeneity are not discussed but could also be important. In a fixed-effect meta-analysis, the assumption is that the same fixed intervention effect is being estimated across all studies. In contrast, in random-effects meta-analysis the assumption is that any intervention effects follow a normal distribution across studies.

For each meta-analysis, heterogeneity among studies was assessed using the I^2 statistic with a cut off value of greater than 40% suggesting heterogeneity (107). The I^2 statistic is a measure used to assess statistical heterogeneity and is preferred to the standard Cochran's Q as it assesses the degree of heterogeneity and is calculated as follows:

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

Equation 14. Calculating the I^2 statistic

Where 'Q' is the Cochran chi-squared test assessing whether observed differences between results are likely to result from chance and 'df' are the degrees of freedom (107). The following is a guide to interpreting the results of the I^2 test:

- Up to 40%: may not be important;
- 40-60%: may represent moderate heterogeneity;
- 60-90%: may represent substantial heterogeneity;
- 90-100%: considerable heterogeneity.

Note that like the Cochran's Q it will have low power when few studies are included.

Dealing with statistical heterogeneity

Several actions were taken when statistical heterogeneity was suspected in the meta-analyses carried out. Firstly, the study-level data was checked to ensure that no inaccuracies had occurred in the data extraction process. Secondly, if the I^2 statistic was above 40% a random-effects method of analysis was used. Statistical heterogeneity was also explored using subgroup analysis. Subgroup analyses were performed based upon clinical and methodological characteristics relevant to the topic of interest in each meta-analysis, details of which are described in relevant chapters (chapters 3-5).

Sensitivity analyses

For each meta-analysis, prespecified sensitivity analyses were performed to test the robustness of the results. Sensitivity analyses used in all systematic reviews included whether or not studies explicitly defined patients with asthma (according to one or more of the following: American Thoracic Society/British Thoracic Society guidelines; reversibility in FEV1 in response to beta2-agonist stimulation; and response to metacholine/histamine provocation challenges), and whether trials stated they withheld beta2-agonists at least 6 hours prior to testing. Additional sensitivity analyses unique to each meta-analysis are described in the relevant chapters.

Quality assessment

Systematic reviews synthesise and collect data on all studies that meet pre-specified eligibility criteria in an attempt to minimise bias. However, bias may still occur because of failings in study design, conduct, analysis and reporting. For each systematic review and meta-analysis, methodological quality and risk of bias were evaluated using the Cochrane Collaboration tool for assessing risk of bias (111). This tool helped to make a decision regarding risk of bias for the following aspects of each trial: blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; random sequence generation; and allocation concealment.

Another important type of bias which may affect the validity of systematic reviews results is publication bias, in which studies with positive findings are more likely to be published than studies with non-significant findings. Publication bias was assessed using funnel plots to examine for asymmetry by creating a simple scatter plot of the effect estimates from individual studies against the standard error of the risk difference

for each study. An asymmetrical appearance is suggestive of publication bias which could result from smaller studies with non-significant findings being unpublished. In circumstances where funnel plot asymmetry was suspected, the Egger test was performed (a form of regression recommended to test for funnel plot asymmetry) (112). The systematic reviews were reported according to PRISMA (Preferred Reporting Items for Systematic Reviews) requirements (113).

2.3 Observational studies using linked electronic health data

This section describes the methodology relating to the pharmacoepidemiology studies reported in this thesis which are:

- Descriptive epidemiology estimating the incidence of asthma exacerbations over a 12 year period
- Drug utilisation studies estimating the prevalence of beta-blocker and NSAID exposure over a 12 year period
- Nested case control studies as the primary analysis for quantifying the risk from exposure to beta-blockers and to NSAIDs (a between-person analysis)
- Self-controlled case series as the secondary analysis for quantifying the risk from acute exposure to beta-blockers and NSAIDs (a within-person analysis)

Specific details unique to each analysis in question are described in chapters 7-9 along with the findings.

2.3.1 Observational studies data source

The pharmacoepidemiology analyses were conducted using electronic primary care health data from the Clinical Practice Research Datalink (CPRD) in the UK, formerly known as the General Practice Research Database. This database was chosen because it

is one of the world's largest longitudinal databases containing electronic medical records from over 680 UK general practices. CPRD has over 11 million patient records, around 5 million of which are currently deemed as being active. CPRD contains linked electronic health care data about patient demographics, prescriptions, clinical events, medical diagnoses, symptoms, hospital referrals, admissions and deaths. Medical diagnoses and clinical events within CPRD are recorded using the Read Code system of classification which is a hierarchical thesaurus of coded clinical terms used in UK primary care electronic records (114).

Recording guidelines are issued to every practice contributing data to CPRD demonstrating the correct method of recording significant morbidity events in each patient's electronic medical record. General practices contributing to CPRD are required to meet defined quality standards of electronic medical record data recording in order to contribute data. Each practice provides raw data which is subject to quality control and validity checking by staff at the Medicines and Healthcare products Regulatory Agency before release. Although principally collected for routine clinical use, data present in CPRD is generally considered to be of high quality with validation studies suggesting that most diagnoses coded in CPRD are well recorded with incidence and prevalence estimates based on CPRD data broadly similar to other UK population-based sources (115, 116).

CPRD contains data on hospitalisation through linkage to the Hospital Episode Statistics (HES) database which contains details of all admissions to NHS hospitals in England. The HES database contains patient care data from admissions occurring from 1989 onwards and is managed by Northgate Information Solutions on behalf of The

NHS Information Centre for health & social care (117). Patients in CPRD are linked to the HES database by means of their NHS number, gender, and partial date of birth.

CPRD also contains mortality data through linkage to the Office for National Statistics (ONS) database for a similar subset of English practices. ONS uses routinely collected information from death certificates in England and Wales which is subject to a number of automatic validation processes to highlight inconsistencies. ONS data is typically first matched to HES data using patient identifiable fields described above and then to practice data within CPRD using probabilistic linkage.

2.3.2 Observational analysis study population

The individual analyses used defined subsets of a broader cohort of adult patients with active asthma. This consisted of patients aged 18 and over present at any point in CPRD between 1 January 2000 and 31 December 2011, who had a Read Code for asthma ever recorded in the patient's electronic medical record *and* had received prescriptions for asthma medication (appendix 2). Subjects were eligible for entry into the cohort if they were permanently registered with a general practice for at least one year prior to cohort entry, had an asthma Read Code ever recorded, were issued two or more prescriptions for asthma medications during their period of registration and were defined by CPRD as being acceptable for use in research (meaning that data contained within their EMR had met certain quality standards). An open cohort design was used and cohort entry was defined: on or after the date of the first asthma medication occurring; on or after 1st January 2000; on or after the patient's 18th birthday; and before the patient's 80th birthday. Asthma medications were defined as: inhaled short-acting beta2-agonists (SABA); inhaled corticosteroids (ICS); inhaled long-acting beta2-agonists (LABA); oral leukotriene antagonists; and oral methylxanthines. Prescriptions for asthma

medication were included in the definition in order to identify patients with active asthma, because asthma remits in some individuals and therefore Read Code recording alone would include some individuals who had not had any asthma related symptoms for many years in which risk may be different.

All patients within this cohort were followed up until the earliest of either: the date of death; deregistration from the practice; one year following the last asthma medication prescribed; or the end of the study period (31 December 2011). Patients recorded with the following diagnoses at any point in their primary care electronic medical record or secondary care Hospital Episodes Statistics (HES) database were excluded from the cohort to minimize misclassification with other respiratory diseases in which beta-blockers and NSAIDs may be better tolerated (appendix 2): chronic obstructive pulmonary disease (COPD); restrictive lung diseases; and bronchiectasis. Patients were also excluded if they had ever been prescribed immunosuppressant therapy (azathioprine, ciclosporin, leflunomide, mercaptopurine, and methotrexate) or had a recorded diagnosis of polymyalgia rheumatica at any point in the electronic medical record. This was done to avoid misclassification of oral steroid use that was not related to asthma. All subjects whose practices were not linked to the HES database of hospitalisation records and ONS database of death registrations were excluded from these analyses so that the different types of event could be evaluated in the same population (complete outcome ascertainment).

2.3.3 Observational analysis outcomes of interest

Asthma events were divided into a hierarchy of events reflecting the severity of the asthma exacerbation namely:

- Asthma death;

- Asthma hospitalisation;
- Primary care asthma exacerbations (PACAE)

Asthma deaths were identified through linkage to the ONS database of death registrations using the International Statistical Classification of Diseases and Related Health Problems 9th and 10th Revision (ICD 9 and 10) codes for asthma as the underlying cause of death (recorded in cause 1, cause 2 or cause 3) as provided by CPRD. This was considered synonymous to part 1a, 1b and 1c of UK ONS requirements for death registration. Hospitalisations for asthma were identified through linkage to the secondary care HES database using ICD10 codes (appendix 2) for asthma recorded as the primary discharge diagnosis (i.e. asthma recorded in the first position) as provided by CPRD. PACAE were defined as the prescription of rescue oral steroid courses where same day prescriptions (duplicate steroid prescriptions) were ignored and classed as single events to avoid clustering. Due to the large variation in steroid regimes and doses used in primary care, patients were only included in the nested case-control analysis of primary care asthma exacerbations if oral steroid prescriptions could be well defined. Patients were therefore excluded from the nested case-control study of PACAE if they were issued any of the following types of oral prednisolone prescriptions during their observation period:

- Prednisolone prescriptions with incomplete information on dosing, frequency and quantity of tablets;
- Prednisolone prescriptions for 1mg or 2.5mg strength tablets suggestive of chronic steroid exposure; and

- Prednisolone prescriptions lasting greater than 2 weeks in duration (calculated by dividing the total quantity of tablets in the prescription by the frequency of tablets recommended each day)

All patients considered as cases therefore had well defined oral steroid prescriptions broadly in keeping with rescue oral steroid treatment doses recommended in guidelines for the management of asthma (2). This was done in order to minimize any potential misclassification related to the outcome of interest.

2.3.4 Observational studies exposures

Beta-blockers were defined according to their selectivity for the beta1-adrenoceptor whilst NSAIDs were defined according to their selectivity to COX1. This was done because the risk of asthma outcomes may differ according to differences in selectivity. The following drugs were considered to be selective beta-blockers (118): acebutolol, atenolol, betaxolol, bisoprolol, celiprolol, and metoprolol. The following drugs were considered to be non-selective beta-blockers: carteolol, carvedilol, labetalol, levobunolol, metipranolol, nadolol, oxprenolol, pindolol, propranolol, sotalol, and timolol. NSAIDs were divided into the following groups according to published IC80 COX-1/COX-2 ratios (91, 119): COX-2 inhibitors (celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib); other NSAIDs with 5-50 fold COX-2 selectivity (etodolac, meloxicam, nimesulide); other NSAIDs with less than 5 fold COX-2 selectivity (diclofenac, piroxicam, mefenamic acid); non-selective NSAIDs (ibuprofen, indomethacin, ketoprofen, naproxen) and aspirin.

All data were anonymised and approval to conduct the study was obtained from the ISAC (Independent Scientific Advisory Committee) for Medicines and Healthcare products Regulatory Agency Database Research (protocol number 12_061R3).

2.3.5 Observational studies primary analysis using nested case control methods

The primary method of analysis used to estimate the association between beta-blocker/NSAID exposure and the incidence of asthma events was the nested case control study (chapters 7-9). I had considered a cohort study with time-dependent variables which provides an absolute measure of association compared to case control studies which traditionally provide a relative measure of association only (120).

However, large cohort studies involving time-dependent variables are computationally demanding and more than one time-dependent variable would need to be adjusted for. I therefore chose the nested case-control study design because controlling for time-dependent confounding is computationally more efficient and can be used to produce odds ratios which reflect unbiased estimators of incidence rate ratios whilst maintaining precision (121). The nested case-control studies in this thesis have four main stages:

1. Accurately defining the cohort (specifically defining cohort entry and eligibility);
2. Following the cohort until the outcome of interest;
3. Generating a risk set involving cases and controls who are present in the cohort at the time of the outcome); and
4. Randomly selecting controls from each risk set.

For each individual analysis, a subset of the CPRD adult active asthma cohort defined above was selected. Details of subset cohort selection for each individual analysis are

provided in each relevant chapter e.g. for the NSAIDs' analysis cohort entry was additionally defined by the prescription of an analgesic (chapter 9). Once cohort entry was established, all patients were followed until either of the following: the first asthma event being studied; death; end of general practice registration; one year following the last asthma medication; or end of the study period (31 December 2011).

Case ascertainment

For all analyses, the date of the first asthma event was the index date for case subjects. A separate nested case-control study was performed for each type of event (asthma death, asthma hospitalisation and PCAE) resulting in three analyses for each exposure of interest.

Control selection

Up to 10 controls were randomly selected and matched to each case on, age (categorised into deciles), gender, calendar year of cohort entry and whether patients were diagnosed with asthma before the age of 45, using incidence density sampling. Incidence density sampling is a technique in which controls present within the cohort are sampled at the exact time of the index event. Therefore, all controls were alive, registered with their general practice when matched to their corresponding case, and had a similar duration of follow-up at the risk set date. The date of the risk set was the index date for the cases and subjects were eligible to be used as controls in multiple sampled risk sets. In addition, controls could later be included as cases, and the same patient could be selected as a control for different cases. When a case could not be matched to one or more controls, the process was repeated matching on gender, calendar year of cohort entry and diagnosis of asthma before the age of 45 only.

Exposures

For all cases and controls, information was obtained on drugs prescribed between cohort entry and the index date including oral beta-blockers and NSAIDs. For cases and controls, beta-blocker and NSAID exposure was categorised into mutually exclusive time periods as follows:

- Current user was defined as a prescription for the exposure of interest issued in the risk window immediately prior to the index date; and
- Nonuser when there was no prescription issued in the risk window immediately prior to the index date.

Current user was further subdivided into;

- Incident user when the prescription was issued in the risk window and no previous prescription was issued in the remaining 365 days prior to the index date; and
- Prevalent user when the prescription was issued during the risk window and also during the remaining 365 days prior to the index date.

In this regard, exposure among incident users corresponds to acute exposure whilst exposure among prevalent users is likely to correspond to chronic exposure. A 30 day, 60 day and 90 day risk window were chosen to assess risk of beta-blocker and NSAID exposure. These risk periods were chosen in order to assess whether risk of exposure attenuates with time and because the exact date the patient started taking the medication was not known.

Among current users, exposure to oral beta-blockers was additionally evaluated according to dose. Low to moderate daily dose and high daily dose of oral beta-blockers were defined using cut-off values based upon beta-blocker equivalency doses published

in heart failure guidelines (122). High dose oral beta-blocker were defined by daily doses greater than the following: acebutolol 200mg, atenolol 50mg, bisoprolol 5mg, carvedilol 25mg, celiprolol 200mg, labetaolol 200mg, metoprolol 100mg, nadolol 80mg, oxprenolol 80mg, pindolol 10mg, propranolol 80mg, sotalol 160mg, and timolol 10mg.

Confounders

For each outcome, an exploratory nested case control analysis using the entire active asthma population matched only on year of cohort entry and whether people were diagnosed with asthma before the age of 45 years was used to determine significant risk factors associated with each asthma event. This analysis excluded beta-blockers and NSAIDs from in the model. This was done in order to inform the choice of potential confounders for subsequent analyses, results of which are presented in chapter 6.

Variables identified as being known potential risk factors for asthma exacerbations and significant confounders were then used for risk adjustment of the crude effect estimates for each event following an assessment of model fit. Model fit was assessed using the Akaike information criterion (AIC) using a smaller is better approach.

The list of variables used for confounding adjustment for each outcome is shown in each analysis chapter (chapters 7-9). A potential list of confounding variables was chosen for assessment a priori. These variables were then assessed for significance in the initial risk factor models presented in chapter 6. Significant variables from this model were then used for confounding adjustment in later analyses. All analyses were adjusted for prescription of the following asthma medications in the 90 days preceding the index date: inhaled corticosteroids (ICS); long-acting beta2-agonists (LABA);

leukotriene antagonists; oral methylxanthines; total number of short-acting beta2-agonists (SABA) prescriptions; and prescription of oral steroids (not included in the PCAE analysis). This was done to adjust for asthma severity whereby people with more severe asthma are treated with asthma medication in a stepwise fashion and because these variables were significant in the initial risk factor models presented in chapter 6. Additional risk adjustment was made for the following in all analyses: whether the patient had ever been hospitalized for asthma; whether there was a recorded respiratory tract infection (RTI) within the risk window prior to the index date; exact age, smoking status (categorised into current, ex-smoker and non-smoker); body mass index (determined as weight/height squared); social deprivation (based upon deciles of the postcode defined Index of Multiple Deprivation); a past medical history of nasal polyps; and the Charlson co-morbidity index. For PCAE additional adjustment was made for attendance at a primary care asthma review within 365 days of the index date because it was significant in the initial model evaluating risk factors for PCAE presented in chapter 6.

The Index of Multiple Deprivation uses data on income, employment, health, education, crime, access to services and living environment to create scores which are ranked into deciles to provide a measure of overall deprivation. The Charlson comorbidity index was used to perform risk adjustment for comorbidity. The Charlson comorbidity index is a widely used and validated index of comorbidity based upon 17 categories of comorbid disease weighted on their association to predict mortality which takes into account the number and severity of conditions (123). The Charlson index was determined from coded diagnoses present in both the CPRD primary care database and the HES database of hospitalisation and calculated using STATA v13. Smoking was

defined by smoking status recorded within three years of the index date. Height and weight were determined as a mean of all adult values recorded in the patient electronic medical record. If smoking status, height or weight was not recorded in the specified time frames, then multiple imputation for missing data was used as described later.

Data management

Multiple imputation is a statistical method for analysing incomplete data sets with the aim of generating valid inferences for statistical estimates from incomplete data.

Multiple imputation has three main stages. The first stage is to randomly generate realistic imputed values to replace missing values in the data set resulting in a number of complete data sets. The second stage is to analyse each imputed data set to generate an statistical estimate and the third stage is to pool these individual estimates into one statistical estimate which combines variation within and between the imputed data sets. Multiple imputation was used to impute missing data on height, weight and smoking status with the assumption that data was missing at random (124). Fully conditional specification is a semi-parametric and flexible approach that specifies the multivariate model by a series of conditional models, on a variable by variable basis. The amount of missing data for each nested case control analysis is presented in each chapter but was generally less than 10%. The imputation model included all variables relating to clinical characteristics, asthma events, asthma medication and the exposure of interest. Multiple imputation was carried out using fully conditional specification, with linear regression for continuous variables and logistic regression for categorical variables using 5 imputed data sets, which is an adequate number based upon a standard approach and the low level of missing data (125). The multiply imputation was performed using the `mi impute chained` command in STATA v13.

Data analysis

Data for cases and controls are presented as means (standard deviation, SD) for continuous variables and as numbers (percentage, %) for categorical variables. Analysis of variance was used to determine significant differences between patient characteristics expressed as a continuous variable. Chi-squared tests were conducted to determine significant differences between patient characteristics expressed as a categorical variable. For differences involving samples with five or less subjects, the Chi-squared test with continuity correction was used to prevent overestimation of statistical significance for small data.

Conditional logistic regression was used to compute odds ratios for the association between events and beta-blocker or NSAID exposure using a 30 day, 60 day and 90 day risk window. These risk periods were chosen in order to assess whether risk of exposure attenuates with time and because the exact date the patient started taking the medication was not known. By using incidence density sampling to select controls the odds ratios are unbiased estimators of incidence rate ratios because the controls are providing an estimate of the proportion of exposed to unexposed person-time. In the primary analysis, current users were compared to nonusers according to selectivity, duration of administration (incident vs. prevalent) and where appropriate by dose. Descriptive analysis was carried out using SPSS v21 and conditional logistic regression using STATA v13.

Sensitivity analyses

For each nested case control analysis, several sensitivity analyses were performed to test the robustness of the results. Firstly, the analysis was repeated by excluding patients

hospitalised within the risk period. This was done because medications prescribed during episodes of hospitalisation are not recorded within CPRD potentially introducing immortal time bias. Secondly, the analysis was repeated by excluding patients over the age of 40 years who smoked and also by excluding patients diagnosed with asthma over the age of 45 years. These two sensitivity analyses were performed to test for any potential misclassification of patients with COPD in which the exposure of interest may be better tolerated (and risk therefore underestimated). Thirdly, the analysis was repeated excluding risk sets in which cases could not originally be matched to controls on age. The number of affected cases is presented in each chapter but generally affected less than 5% of cases. Lastly, a complete case analysis was performed and compared to the analysis using multiply imputed data.

2.3.6 Observational studies secondary analysis using self-controlled case series methods

For each nested case control study a secondary analysis using the self-controlled case series method was used to determine whether consistency in results was seen using a different method. This method was chosen because it can be used to investigate risk associated with incident (acute) exposures whilst at the same time eliminating fixed within-person confounding which may still be present in the nested case control study design. The nested case-control study is a between-person design where the relative incidence of events is estimated between different subjects using a risk window. In contrast, the self-controlled case-series (SCCS) is a within-person design where the relative incidence of events is compared between periods of exposure and non-exposure in the same individual (126). As such, each person acts as their own control and analysis only uses individuals who are cases (i.e. people with the event of interest). In this way

all fixed within-person confounding relating to factors such as gender, social deprivation and genetics are eliminated although the analysis can still be affected by time-dependent confounding. A case-exposure SCCS design was used in which only cases with incident beta-blocker or NSAID exposure were evaluated.

Observation period

The SCCS was conducted over a 360 day time period during which events are assumed to occur according to a non-homogenous Poisson distribution (126). The beginning of the observation period was defined as 180 days prior to the date of an incident prescription for the exposure of interest (defined as above as the prescription of a beta-blocker or NSAID with no prescription of the same drug class in the 365 days prior to the index prescription) and the end of the observation period was defined as 180 days following this incident prescription. For each patient, incident exposure was defined as the first beta-blocker or NSAID prescription in the file in people with at least 1 year of follow up prior to the first prescription. In this regard, all patients used in the SCCS analysis were cases who had the exposure of interest.

Events

One limitation of the SCCS is that it requires that the probability of exposure is not affected by the occurrence of an event. This assumption is required for the conditioning argument that is used to derive the case series likelihood. The greatest threat to this assumption is when the outcome is a censoring event such as death. For this reason, the event of interest chosen for the SCCS analyses presented in this thesis was restricted to PCAEs (a frequent recurrent event) using a pre-risk period to account for potentially short-lived event dependent exposures (detail provided below). PCAEs were defined by

rescue oral steroid prescriptions occurring during the study period as defined above.

Oral steroid prescriptions issued within fourteen days of each other were considered to be for the same event in order to avoid clustering and potential overestimation of the relative incidence.

Risk periods

The greatest risk from beta-blocker and NSAID in asthma is typically thought to result from incident (acute) exposure. The nested case-control study evaluated three risk windows covering a 30 day, 60 day and 90 day period respectively. To establish whether the incidence of PCAE increased immediately following incident prescription, three risk periods of the same duration were defined in the SCCS. The start date for the risk period was the date of the incident beta-blocker or NSAID prescription among cases. These risk periods were chosen so that results could be directly comparable to the nested case control study.

The end of beta-blocker or NSAID exposure was determined by estimating exposure duration using prescriptions issued within the observation period. The estimated duration was calculated by dividing the total quantity of tablets in the prescription by the frequency of tablets recommended each day. In a minority of instances duration could not be calculated due to missing prescription information, in which case prescription duration of 28 days was assumed and imputed. For the purpose of this analysis, exposure extending beyond the acute risk period was defined as chronic exposure.

Because it is unlikely that people with asthma will be prescribed beta-blockers or NSAIDs for the first time during an asthma exacerbation, an immediate 30 day pre-risk period was defined. Person time and events occurring within the pre-risk period were then excluded from the analysis to account for possible short-lived event-dependent exposures between primary care asthma exacerbations and the exposure of interest. Failure to account for this in the design potentially overestimates the relative incidence of events because baseline incidence is reduced producing a biased result (126). A description of the SCCS method used is shown in figure 1. Incident exposure (representing the acute risk period) was centred within the 360 day observation period (chosen to reduce the potential impact of time-varying confounding and because investigating the acute risk period was the primary focus). If exposure extended beyond the acute risk period it was classed as prevalent exposure and partitioned as shown below. Apart from the pre-risk period which accounts for short lived event dependent exposures, all remaining time was classed as baseline observation. The incidence of events was then counted between periods of exposure and non-exposure within the same individual. Prescriptions issued during periods of hospitalisation are not recorded in CPRD which potentially introduces immortal time bias. For this reason, any hospitalisations occurring during the SCCS study period were identified and the duration of hospitalisation calculated. This person time was then subtracted from the corresponding exposure group.

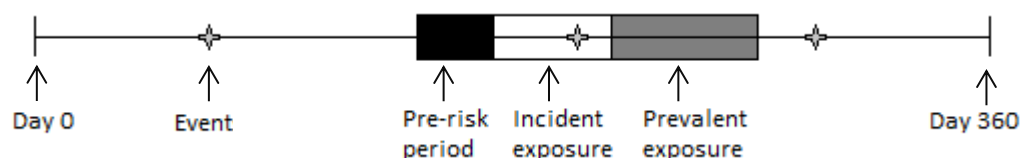


Figure 1. Diagrammatic representation of the self-controlled case series design used.

Confounders

Although the SCCS controls for all time-fixed confounding, it does not account for time-varying confounding. In order to reduce the potential impact of time-varying confounding, the study observation period was restricted to a 360 day time period centred on the exposure of interest. Time-varying exposure to the following medications issued within each 90 day consecutive period was then adjusted for in the analysis: ICS; inhaled LABAs; leukotriene antagonists; methlyxanthines; and the total number of SABA prescriptions. Additional risk adjustment was also made for seasonal variation.

Data analysis

Data for cases are presented as means for continuous variables and as numbers (percentage, %) for categorical variables. The SCCS was analysed using conditional Poisson regression producing incidence rate ratios, with analyses stratified by selectivity as well as by dose where appropriate (126). Although age in years is unlikely to have a significant impact over a one year observational period, the impact of adjusting for age in the model was investigated by introducing an age term after 180 days of the study period. However, for this analysis age was not found to be a significant time-varying confounder and inclusion of age caused a worse model fit as assessed by the AIC. Age effects were therefore not included in the final model. Descriptive analysis was carried out using SPSS v21 and conditional Poisson regression using STATA v13.

2.4 Summary

The first half of this chapter describes the general systematic review and meta-analysis methodology used to evaluate the adverse respiratory effect of beta-blockers and NSAIDs using existing clinical trial evidence with strong internal validity with results presented in chapters 3-5. The second half of this chapter describes the population used to measure the risk from beta-blocker and NSAID prescribing, with the primary analysis using the nested case control study and secondary analysis using self-controlled case series to quantify the frequency and severity of adverse respiratory events among people with asthma. The results from these observational studies are presented in chapters 7-9. All studies have some individual elements of methods, for example in terms of the cohort definitions in the observational analyses, and these are described in the individual results chapters where appropriate.

Chapter 3: Acute Beta-Blocker Exposure in Asthma: Systematic Review and Meta-Analysis of Controlled Clinical Trials

3.1 Introduction

The first half of this thesis focuses on synthesising clinical trial evidence for the exposure of interest because this type of evidence has strong internal validity. This chapter will synthesise clinical trial evidence evaluating acute beta-blocker exposure on respiratory function in people with asthma. Beta-blockers cause bronchoconstriction in people with asthma as a result of antagonising the effects of catecholamines at the pulmonary beta2-adrenoceptor which alters the balance between sympathetic and parasympathetic drive controlling airway smooth muscle tone. A previous systematic review has been performed evaluating beta-blockers in people with reversible airways disease (consisting of asthma and COPD). That systematic review included 19 trials evaluating single-dose treatment with selective beta-blockers and reported a 7.5% mean fall in FEV1, a 4.6% increase in FEV1 following beta2-agonist, and no significant increase in respiratory symptoms compared to placebo (87). However, the degree of fall in FEV1 following exposure may also vary according to individual susceptibility. From this perspective, a small change in mean FEV1 in the whole population might be consistent with a minority of individuals having large and clinically significant falls, and this analysis therefore also evaluates the proportion of participants with a $\geq 20\%$ fall in FEV1 and the proportion experiencing respiratory symptoms in addition to mean changes in FEV1.

These potential effects were not evaluated in the previous systematic review, nor were variation by beta-blocker selectivity. It is known that there are differences in the degree of beta1:beta2-adrenoceptor selectivity among individual selective beta-blockers, and subtype selectivity may vary according to dose. Selective beta-blockers, which the previous systematic review focused on, are not the only type of beta-blocker which need

evaluating because the cross-sectional study I conducted as pilot work demonstrated that 1.1% of adults with asthma were prescribed non-selective beta-blockers over the course of a year (84). Also, other types of beta-blockers are indicated for certain conditions, but are often avoided in people with asthma. For instance, the non-selective beta-blocker and alpha-blocker labetalol is a first-line treatment for pregnancy-induced hypertension but is contraindicated in asthma (127).

Finally, beta2-agonists are typically considered first-line rescue therapy for the management of acute bronchoconstriction in asthma and in theory their efficacy could be reduced when co-administered with beta-blockers. Even if beta-blockers were well tolerated, blunting the beta2-agonist response during episodes of bronchoconstriction triggered by other factors would be hazardous. However, the previous systematic review demonstrated a 4.6% increase in FEV1 with beta2-agonist compared to placebo following administration of single dosing with selective beta-blockers which is surprising given the pathophysiology. In contrast, beta2-agonist response in the presence of non-selective beta-blockade has not previously been systematically reviewed.

3.2 Aim

The first aim of this analysis was to quantify the changes in lung function which occur following acute beta-blocker exposure and to assess the incidence of respiratory symptoms among people with asthma. The second aim of this chapter was to determine the efficacy of beta2-agonists following acute beta-blocker exposure to better inform their use in people with asthma.

3.3 Methodology

Search strategy and selection criteria

The systematic review was conducted using methodology described in the general methods chapter (chapter 2, page 50). A pre-specified search strategy (appendix 1) was used to search MEDLINE, EMBASE and CENTRAL databases. The PICOS approach used in this chapter is described in table 2. Beta-blockers were evaluated in people with asthma and people with COPD were excluded. Studies evaluating exposure in people with prior beta-blocker sensitivity were excluded because these people have a different risk of bronchospasm and are not representative of all people with asthma. Studies evaluating acute exposure to oral, intravenous or topical beta-blockers through the use of randomised, blinded, placebo-controlled trials were eligible for inclusion. Acute exposure was defined as exposure lasting under 7 days. Dichotomous outcomes included fall in FEV1 of 20% or greater and respiratory symptoms. Continuous outcomes included mean fall in FEV1.

Table 2. PICOS approach used for the beta-blocker systematic review.

Population	Included	Patients with asthma*
	Excluded	Patients with COPD ^Ω and healthy patients
Intervention	Included	Oral, intravenous or topical beta-blocker exposure
	Excluded	Inhaled beta-blocker exposure
Comparator	Included	Placebo
Outcomes	Included	Symptoms
		Fall in FEV1 $\geq 20\%$
		Mean per cent change in FEV1
		FEV1 response to beta2-agonist
	Excluded	Other measures of airway resistance
Studies	Included	Randomized controlled trials in humans
		Single or double-blinded
		Selection not based on prior response [¥]

^ΩCOPD = emphysema and chronic bronchitis

Data processing and extraction

Data processing and extraction followed the standard methodology set out in the general methods chapter (chapter 2, page 52).

Data analysis

Data analysis followed the standard methodology set out in the general methods chapter (chapter 2, page 52). Mean fall in FEV1 was presented as the absolute mean percentage difference in FEV1, compared to placebo. Falls in FEV1 of 20% or greater and respiratory symptoms were presented as the risk difference, compared to placebo.

Beta2-agonist response was calculated immediately following administration of beta-blockers or placebo and presented as the mean percentage difference in FEV1. All changes in FEV1 were calculated relative to baseline FEV1 values. Subgroup analyses were performed to evaluate the mean fall in FEV1 for individual drugs and dose-response relationships where feasible. These subgroup analyses were chosen because beta-blockers differ in beta1:beta2-adrenoceptor subtype selectivity within class and response may also vary by dose of exposure. Subgroup analysis was performed for the following individual drugs: atenolol, celiprolol, labetalol, metoprolol, and propranolol. Dose response was assessed for atenolol, bisoprolol and metoprolol. This could not be done for all drugs due to the limited number of trials. A random-effects method of analysis was performed because significant heterogeneity was detected using the I^2 statistic (>50%).

Sensitivity analyses

Sensitivity analyses were performed for mean change in FEV1 restricting attention to studies using different definitions of asthma (whether asthma was simply stated to be present or was explicitly defined according to one or more of American Thoracic

Society/British Thoracic Society guideline criteria, reversibility in FEV1 in response to beta2-agonists, or through bronchial provocation challenge testing) and whether or not studies withheld beta2-agonists for at least 6 hours (chapter 2, page 63). Further sensitivity analysis was performed evaluating mean change in FEV1 using the minimum and maximum p-values for the calculation of missing standard deviations (chapter 2, page 60).

3.4 Results

Of 1989 references screened 32 studies evaluating acute oral or intravenous beta-blocker exposure were included in the main analysis (figure 2 and table 3). Sixteen studies evaluated selective beta-blockers, 6 studies evaluated non-selective beta-blockers and 10 studies evaluated both selective and non-selective agents. No randomized blinded placebo-controlled studies evaluating acute topical beta-blockers in patients unselected on the basis of prior exposure were found, and topical beta-blockers are not further considered. For selective oral or intravenous beta-blockers, a total of 23 studies provided data on mean per cent change in FEV1, 13 studies provided data on symptoms, 5 studies provided data on fall in FEV1 of 20% or greater and 17 studies provided data on beta2-agonist response. For non-selective oral or intravenous beta-blockers, a total of 14 studies provided data on mean per cent change in FEV1, 6 studies provided data on symptoms, 3 studies provided data on fall in FEV1 of 20% or greater and 9 studies provided data on beta2-agonist response.

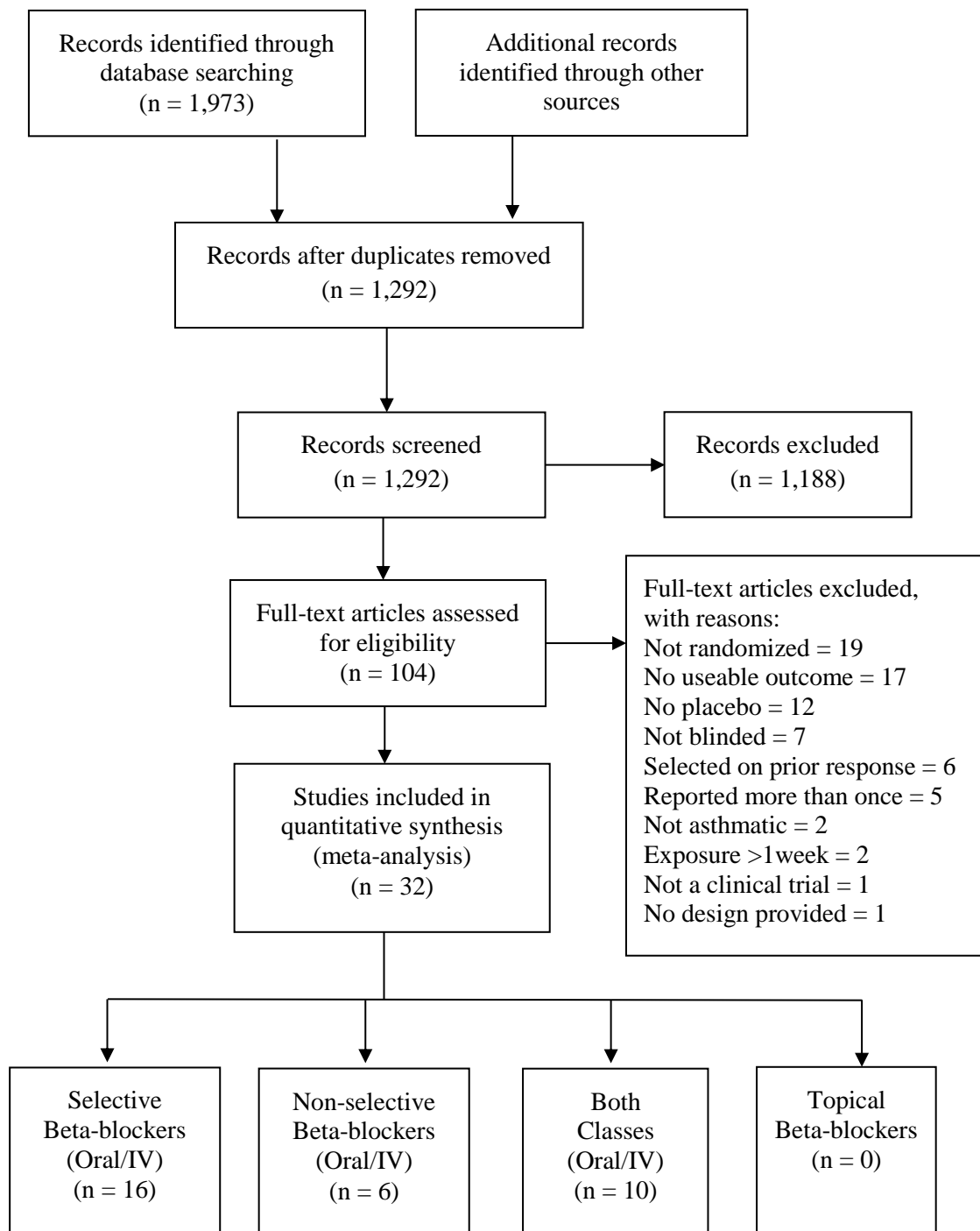


Figure 2. PRISMA flow diagram for study selection in the beta-blocker systematic review.

Table 3. Characteristics of included studies in the beta-blocker systematic review.

Study ^(reference)	Exposure	Patients	Route	Asthma [¥]	SABA ^Ω	Outcome	Beta-blocker Exposure
Benson 1978 ⁽¹²⁸⁾	SD	12	O	Yes	Yes	M, S	Atenolol, Propranolol, Pindolol
Beumer 1978 ⁽¹²⁹⁾	SD	12	O	Yes	No	M	Propranolol, pindolol, mepindolol
Boye 1977 ⁽¹³⁰⁾	SD	10	IV	No	No	M	Atenolol
Cannon 1982 ⁽¹³¹⁾	SD	15	O	Yes	No	S, F	Pindolol
Chatterjee 1986 ⁽¹³²⁾	SD	12	O	Yes	Yes	M, S	Atenolol, bisoprolol
Chodosh 1988 ⁽¹³³⁾	SD	16	O	Yes	Yes	M, S, F	Metoprolol, dilevalol
Dal Negro 2002 ⁽¹³⁴⁾	SD	12	O	Yes	Yes	M, S	Nebivolol
Devereux 1998 ⁽¹³⁵⁾	SD	16	O	Yes	Yes	M, S	Sotalol
Doshan 1986 A ⁽¹³⁶⁾	SD	15	O	Yes	Yes	M	Atenolol, celiprolol
Doshan 1986 B ⁽¹³⁷⁾	SD	34	O	Yes	Yes	M	Atenolol, celiprolol, propranolol
Ellis 1981 ⁽¹³⁸⁾	SD	10	O	No	Yes	M	Atenolol, propranolol
Ellis 1984 ⁽¹³⁹⁾	SD	8	O	Yes	Yes	M, S, F	Atenolol, metoprolol
Falliers 1985 ^δ ⁽¹⁴⁰⁾	SD	18	O	Yes	Yes	M	Labetalol
Falliers 1986 ⁽¹⁴¹⁾	SD	18	O	Yes	Yes	M	Metoprolol, labetalol
Fogari 1990 ⁽¹⁴²⁾	7 days	10	O	Yes	Yes	M, S	Atenolol, celiprolol, propranolol, oxprenolol
Jackson 1983 ⁽¹⁴³⁾	SD	11	O	No	Yes	M, F	Atenolol, labetalol
Lammers 1985 ⁽¹⁴⁴⁾	SD	8	O	Yes	Yes	M	Atenolol, bevantolol
Larsson 1982 ⁽¹⁴⁵⁾	SD	14	IV	No	Yes	M, S	Propranolol, labetalol, practolol
Lawrence 1982* ⁽¹⁴⁶⁾	SD	14	O	Yes	Yes	M, S	Atenolol, metoprolol, propranolol
Lofdhal 1981 ⁽¹⁴⁷⁾	SD	8	O	Yes	Yes	M	Atenolol, metoprolol
Lofdhal 1988 ⁽¹⁴⁸⁾	SD	10	O	Yes	Yes	S	Atenolol, metoprolol
Matthys 1985* ^δ ⁽¹⁴⁹⁾	SD	12	O	No	Yes	M	Celiprolol, propranolol

Mue 1979 ⁽¹⁵⁰⁾	SD	34	O	Yes	Yes	S	Acebutolol
Nair 1981 ⁽¹⁵¹⁾	2 days	10	O	No	Yes	M	Acebutolol
Nicolaescu 1972 ⁽¹⁵²⁾	3 days	10	O	Yes	Yes	M, S, F	Practolol
Nicolaescu 1973 ⁽¹⁵³⁾	3 days	10	O	Yes	Yes	M, S, F	Practolol
Repsher 1986 ⁽¹⁵⁴⁾	SD	18	O	Yes	Yes	M, S	Metoprolol, labetalol
Skinner 1975 ⁽¹⁵⁵⁾	SD	10	IV	No	Yes	M	Propranolol, labetalol
Sue 1982* ⁽¹⁵⁶⁾	SD	23	IV	No	No	M	Pindolol
Suzuki 1981 ⁽¹⁵⁷⁾	SD	24	O	Yes	Yes	M	Atenolol
Tantucci 1990 ⁽¹⁵⁸⁾	SD	12	O	No	Yes	M, S	Atenolol, metoprolol
Thiringer 1976 ⁽¹⁵⁹⁾	SD	8	O	Yes	Yes	M	Metoprolol, practolol, propranolol

[‡] Whether or not studies defined asthma as per ATS/BTS guidelines, reversibility of $\geq 15\%$ in response to SABA or positive histamine/metacholine provocation test. ^Ω Whether or not studies withheld short-acting beta2-agonists (SABA) for at least 6 hours. * Data combined from duplicated studies in Lawrence 1983 (160), Matthys 1986 (161), and Sue 1981 (162). ^δ Studies used in subgroup analysis of celiprolol and labetalol only as patients selected on basis of prior sensitivity to propranolol. SD = single dose; O = oral; IV = intravenous; + = yes; - = no. Oxpr=oxprenolol. M = mean change in FEV1. S = symptoms. F = FEV1 fall $\geq 20\%$.

Table 4. Dose range of beta-blockers from included studies.

Beta-blocker	Oral	IV
Selective		
Acebutolol	300-400mg	-
Atenolol	50-200mg	3mg
Bevantolol	400mg	-
Bisoprolol	10-20mg	-
Celiprolol	200-600mg	-
Dilevalol	400mg	-
Metoprolol	50-200mg	-
Nebivolol	5mg	-
Practolol	200mg	10mg
Non-selective		
Labetalol	100-400mg	20mg
Mepindolol	5mg	-
Oxprenolol	80-100mg	-
Pindolol	5-15mg	0.4mg
Propranolol	40-100mg	5mg
Sotalol	240mg	-
Timolol	10mg	-

The most common selective beta-blockers evaluated were atenolol (15 studies) and metoprolol (9 studies) and the most common non-selective beta-blockers to be evaluated were propranolol (9 studies) and labetalol (6 studies, tables 3 and 4). For oral and intravenous administration, a total of 600 acute selective beta-blocker exposures were evaluated in 330 patients with asthma (mean age 46 years, 67.5% male). A total of 301 acute non-selective beta-blocker exposures were evaluated in 218 patients with asthma (mean age 40.5 years, 68.9% male). Mean baseline FEV1 for patients exposed to selective and non-selective beta-blockers were 2.28L and 2.50L respectively. Of the trials identified 28 (88%) were single-dose studies with respiratory measurements taken on average 108 minutes post-dose.

Acute selective beta-blockade

Compared to control, acute selective beta-blocker exposure caused a mean percentage change in FEV1 of -6.9% (95% CI -8.5 to -5.2, $p < 0.01$ figure 3) with an I^2 statistic of 23% ($p = 0.16$). The risk difference for fall in FEV1 of 20% or greater was 0.13 (95% CI 0.01 to 0.24, $p = 0.03$ figure 4) equating to a number needed to treat of 8 to produce a fall in FEV1 of 20% or greater in one person. The risk difference for symptoms was 0.03 (95% CI -0.01 to 0.06, $p = 0.18$ figure 5) equating to a number needed to treat of 33 to cause symptoms in one person but was not statistically significant compared to control.

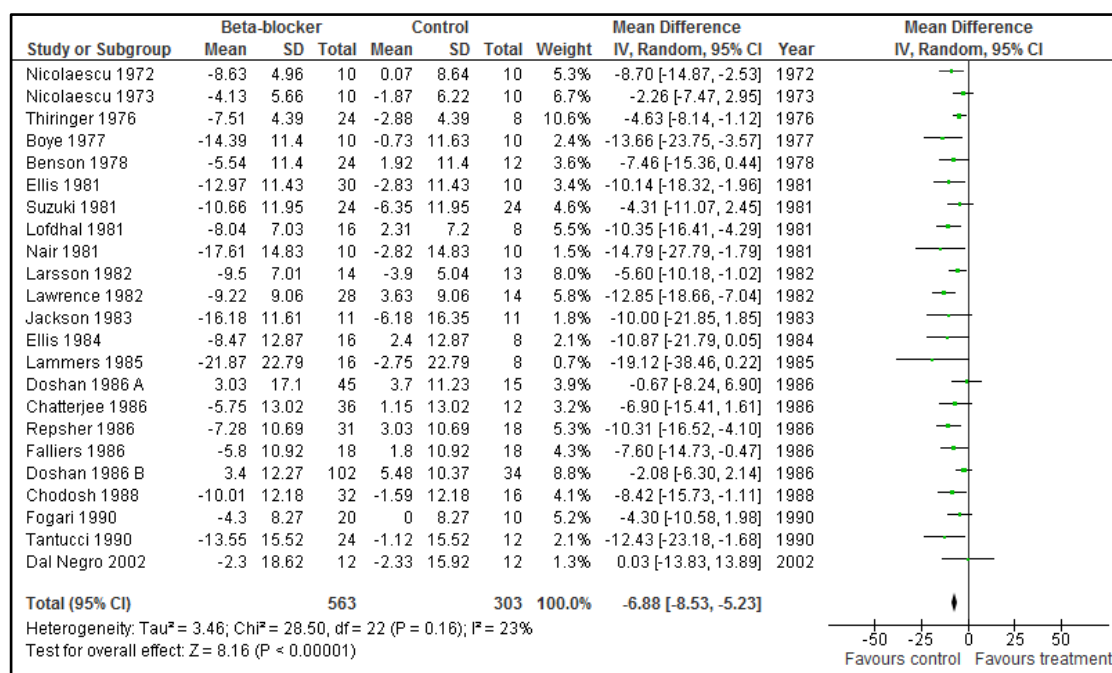


Figure 3. Mean percentage change in FEV1 following acute selective beta-blocker exposure.

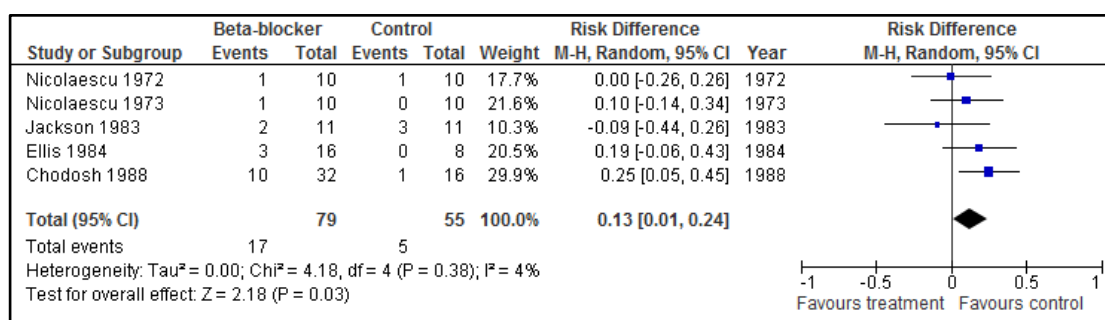


Figure 4. Fall in FEV1 of 20% or greater following acute selective beta-blocker exposure.

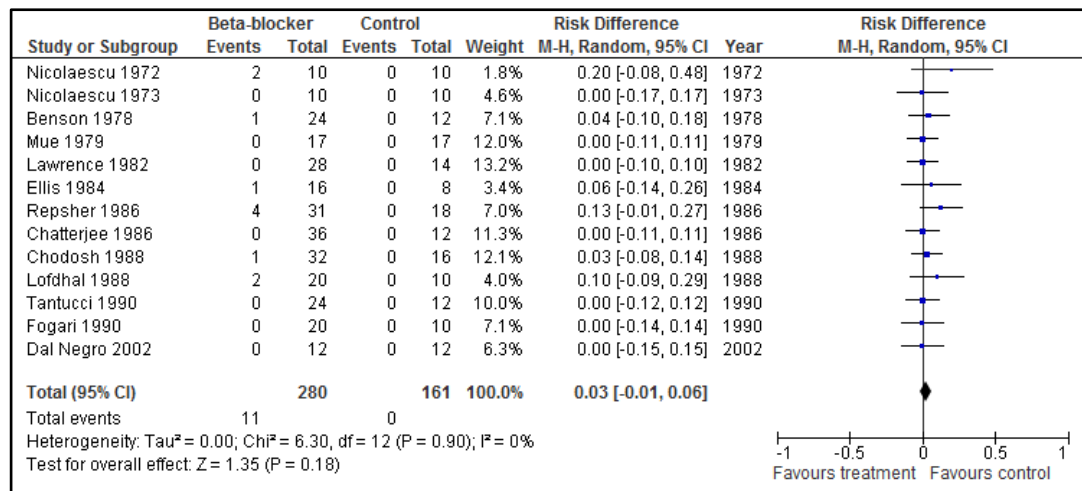


Figure 5. Symptoms following acute selective beta-blocker exposure.

Acute non-selective beta-blockade

Compared to control, acute non-selective beta-blocker exposure caused a mean percentage change in FEV1 of -10.2% (95% CI -14.7 to -5.6, $p < 0.01$ figure 6) with an I^2 statistic of 84% ($p < 0.0001$). The risk difference for fall in FEV1 of 20% or greater was 0.11 (95% CI -0.04 to 0.26, $p = 0.14$ figure 7) equating to a number needed to treat of 9 to cause a fall in FEV1 of 20% or greater in one person, which was not statistically significant compared to control. The risk difference for symptoms was 0.08 (95% CI 0.01 to 0.15, $p = 0.02$ figure 8) equating to a number needed to treat of 13 to cause symptoms in one person.

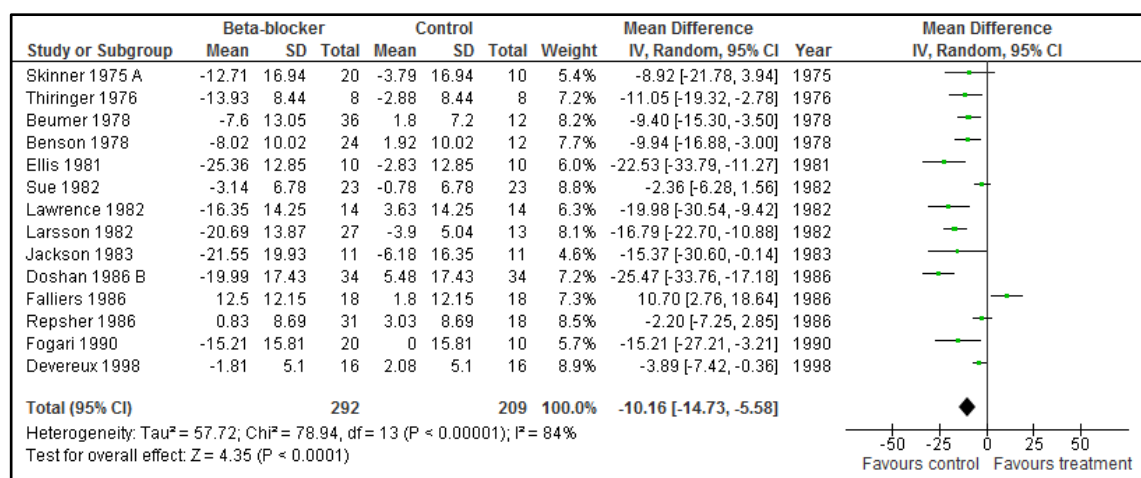


Figure 6. Mean percentage change in FEV1 following acute non-selective beta-blocker exposure.

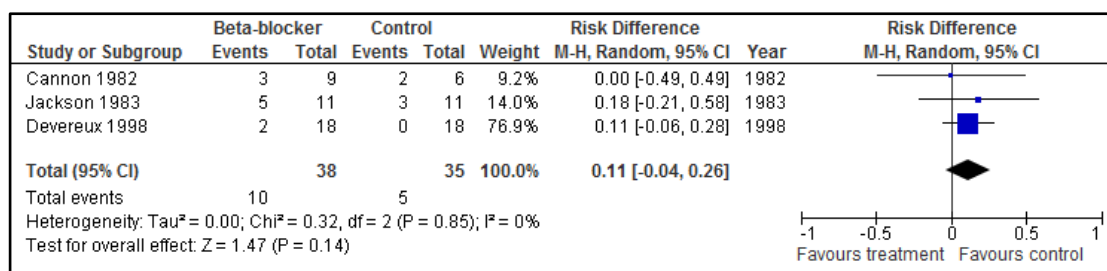


Figure 7. Fall in FEV1 of 20% or greater following acute non-selective beta-blocker exposure.

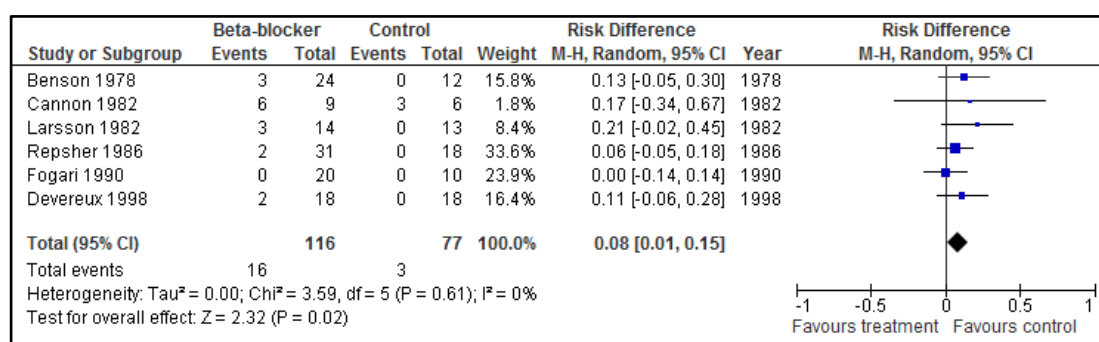


Figure 8. Symptoms following acute non-selective beta-blocker exposure.

Beta2-agonist response following acute beta-blockade

Compared to control, acute selective beta-blocker exposure caused a mean percentage change in FEV1 following SABA stimulation of -10.2% (95%CI -14.0 to -6.4, $p < 0.01$ figure 9) relative to baseline with an I^2 statistic of 64% ($p < 0.001$). This means that acute exposure to selective beta-blockers blunted the FEV1 response to beta2-agonists by 10.2%. Compared to control, acute non-selective beta-blocker exposure caused a mean percentage change in FEV1 following SABA stimulation of -20.0% (95%CI -29.4 to -10.7, figure 10) relative to baseline with an I^2 statistic of 90% ($p < 0.001$). This means that acute exposure to non-selective beta-blockers blunted the FEV1 response to beta2-agonists by 20.0%. Response to beta2-agonist is summarised in figure 11. Following selective and non-selective beta-blockers mean FEV1 was -6.9% and -10.2% respectively. Following the administration of beta2-agonist, mean FEV1 response was

+22.7% for placebo, +16.0% following exposure to selective beta-blockers, and -0.7% following exposure to non-selective beta-blockers.

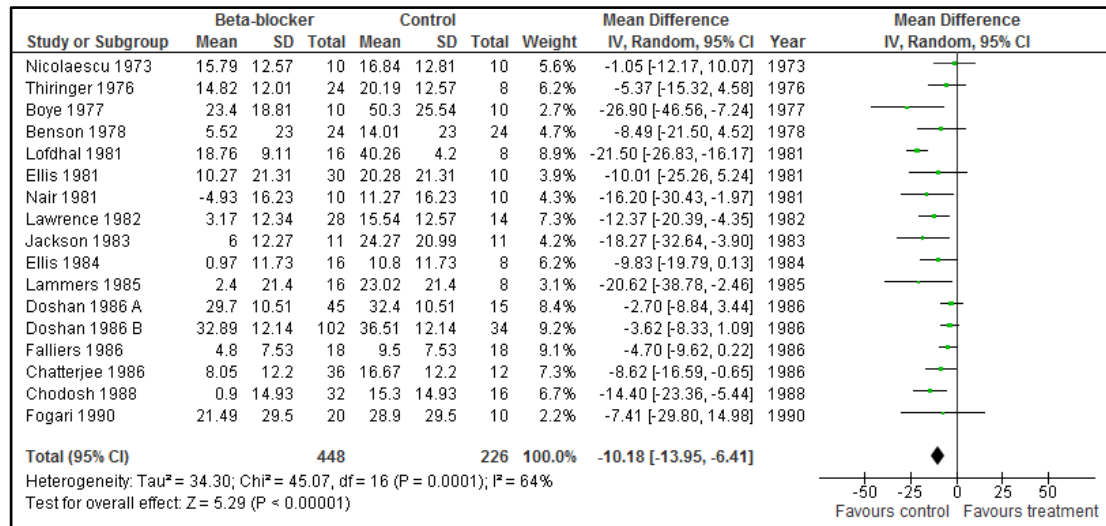


Figure 9. Mean percentage difference in response to beta2-agonist following acute selective beta-blockade.

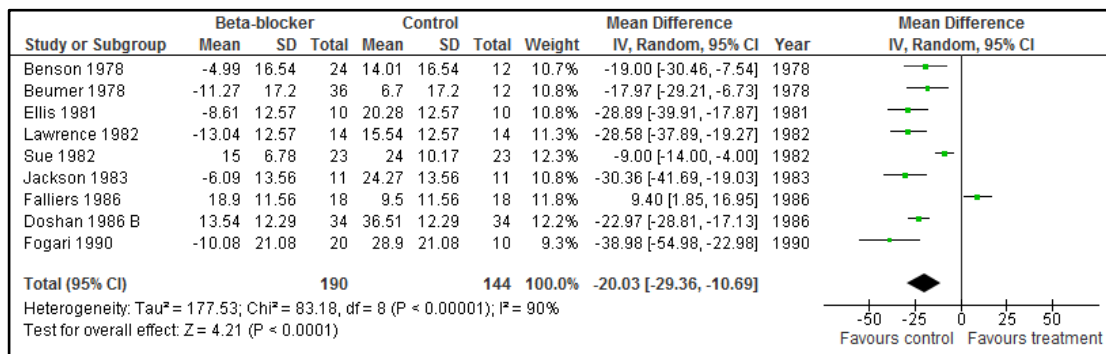


Figure 10. Mean percentage difference in response to beta2-agonist following acute non-selective beta-blockade.

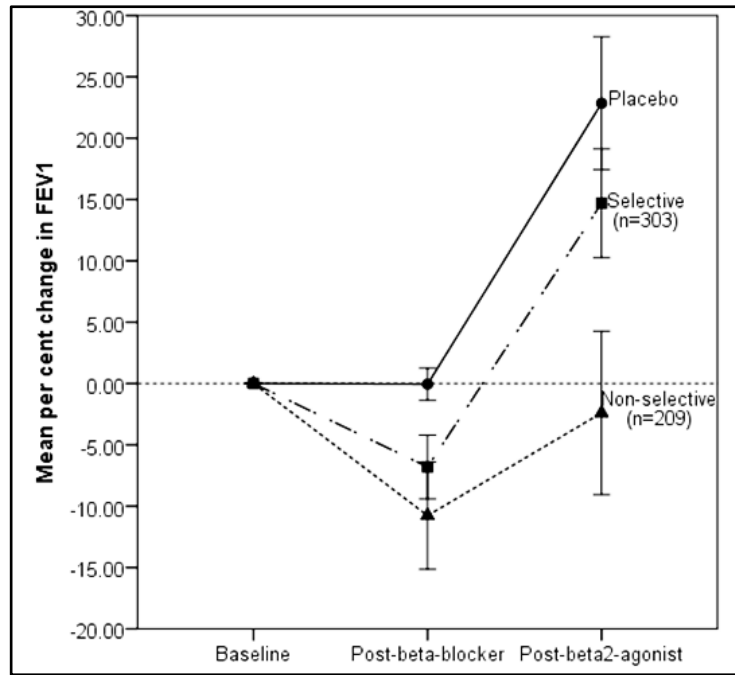


Figure 11. Mean percentage change in FEV1 and response to beta2-agonist relative to baseline following acute beta-blocker exposure.

N=number of participants.

Subgroup analysis

Individual selective beta-blocker comparisons

Selective beta-blockers appeared to vary to the degree of fall in FEV1 following acute exposure. For selective beta-blockers, celiprolol appeared to have the least effect on FEV1 whilst acebutolol had the greatest (figure 12). Among each class of beta-blocker, individual agents had similar patterns of response to beta2-agonists but varied in size of that response. In this respect, beta2-agonists caused an increase in FEV1 with all selective beta-blockers typically causing an increase in FEV1 well beyond baseline levels.

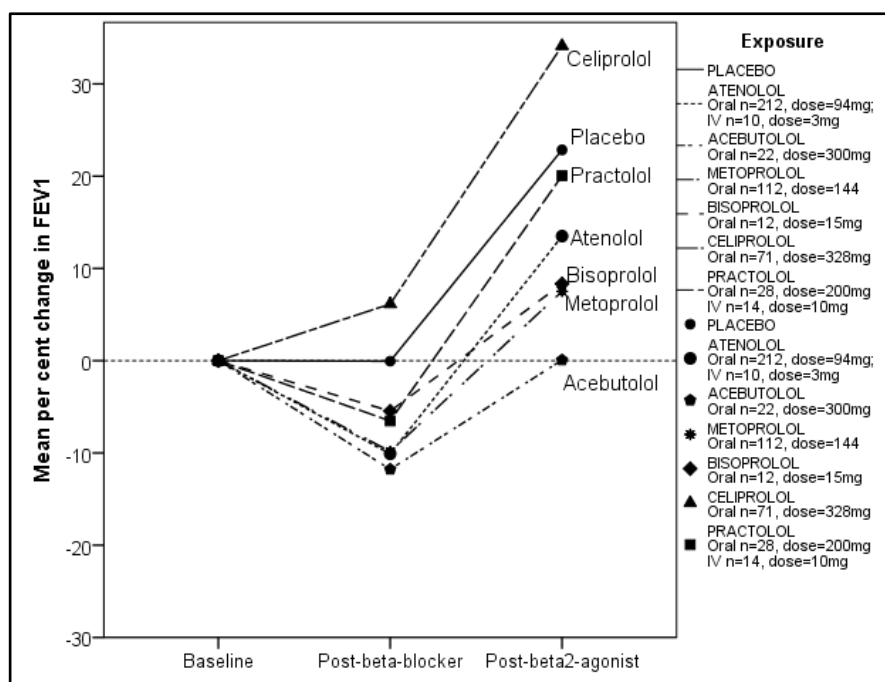


Figure 12. Mean percentage change in FEV1 and response to beta2-agonist relative to baseline following acute selective beta-blocker exposure.

*Baseline represented by dotted line. Dose = mean dose; N = number of participants.

Sufficient data was available to evaluate mean percent change in FEV1 for several selective beta-blockers. Celiprolol caused a mean percentage change in FEV1 of 1.8% (95% CI -2.3 to 5.8, figure 13). In comparison, metoprolol caused a mean percentage change in FEV1 of -9.3% (95% CI -12.0 to -6.6, figure 14) and atenolol caused a mean percentage change in FEV1 of -10.2% (95% CI -12.6 to -7.8, figure 15). There was sufficient data to evaluate a dose-response relationship for metoprolol, atenolol and bisoprolol which showed an increasing dose-response relationship (figures 16 to 18). Mean percentage change in FEV1 following acute exposure to 50mg, 100mg and 200mg of metoprolol was -6.0%, -8.9% and -13.0% respectively. Mean percentage change in FEV1 following acute exposure to 50mg, 100mg, and 200mg of atenolol was -5.4%, -11.4% and -10.9% respectively. Mean percentage change in FEV1 following acute exposure to 10mg and 20mg of bisoprolol was -5.8% and -7.5% respectively.

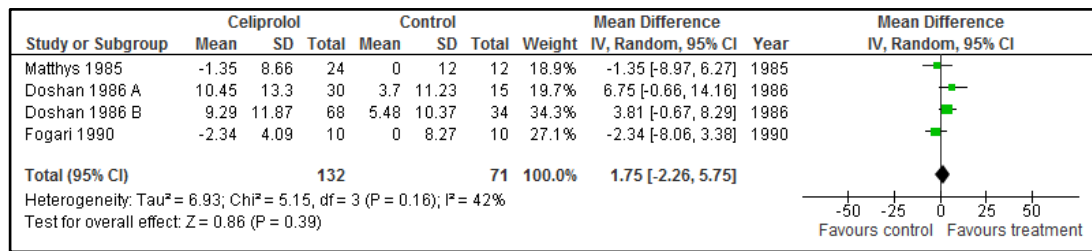


Figure 13. Mean percentage change in FEV1 following acute celiprolol exposure.

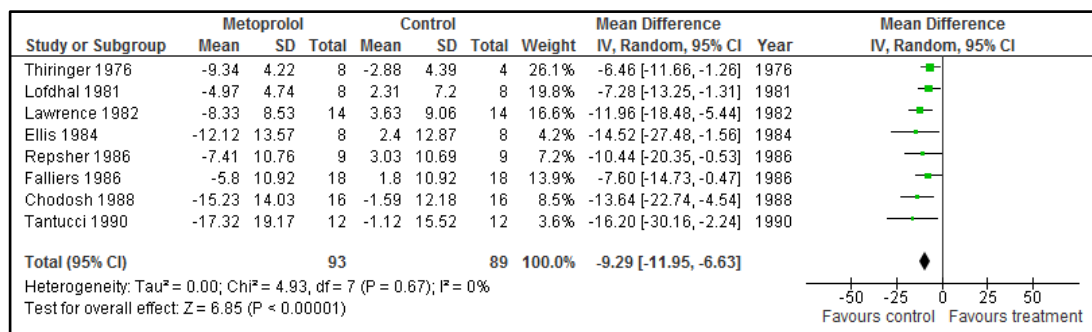


Figure 14. Mean percentage change in FEV1 following acute metoprolol exposure.

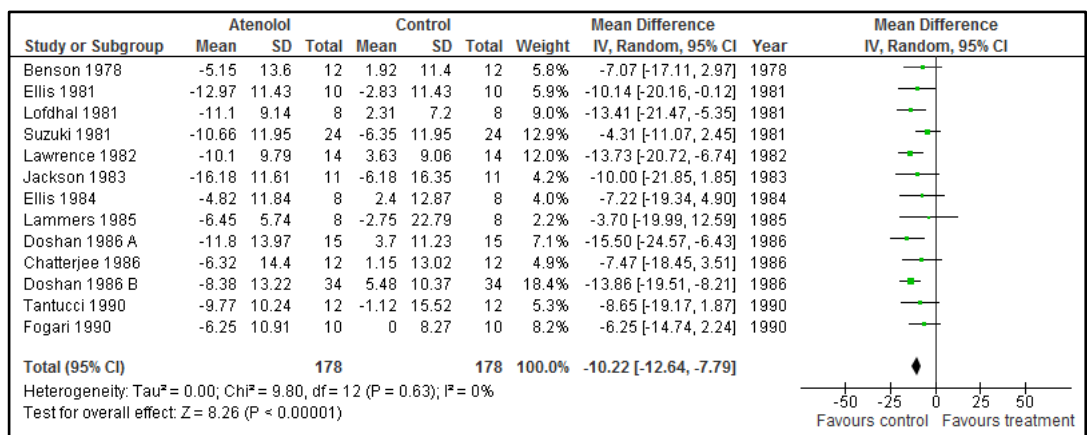


Figure 15. Mean percentage change in FEV1 following acute atenolol exposure.

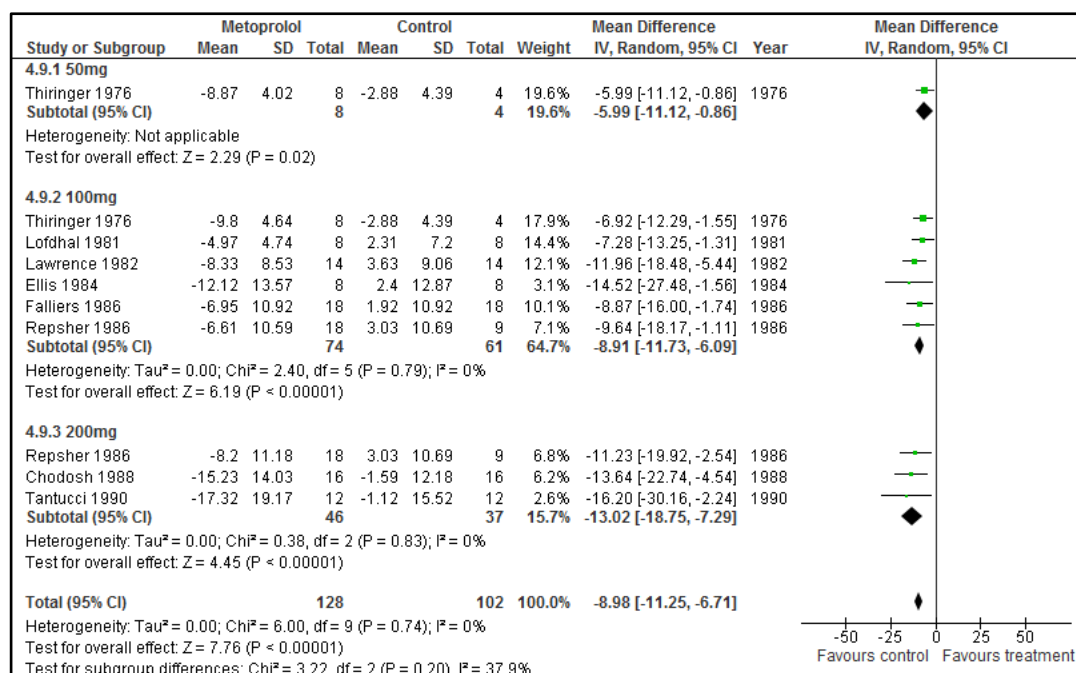


Figure 16. Dose response relationship for metoprolol (mean change in FEV1).

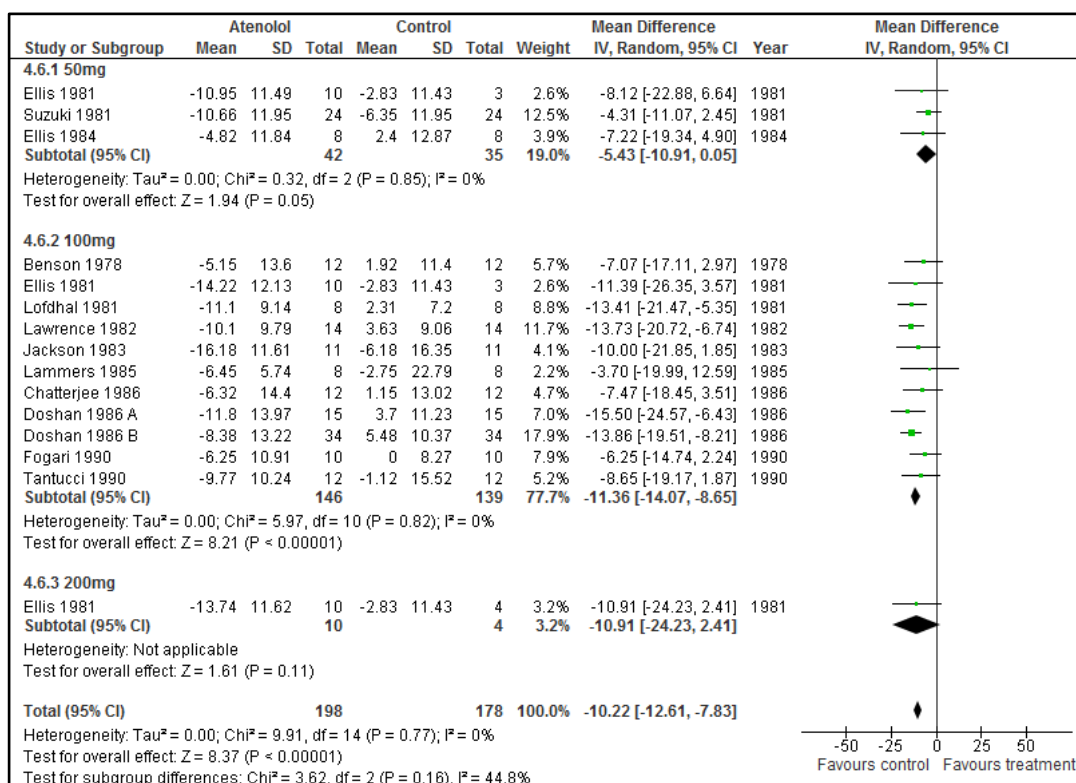


Figure 17. Dose response relationship for atenolol (mean change in FEV1).

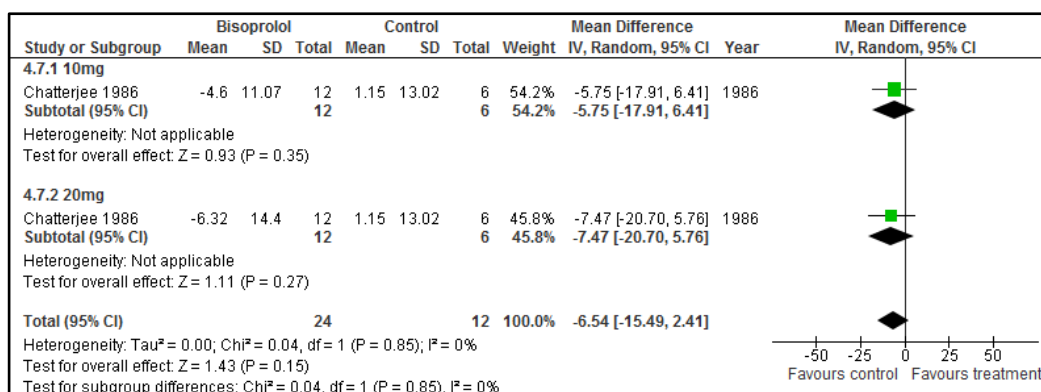


Figure 18. Dose response relationship for bisoprolol (mean change in FEV1).

Individual non-selective beta-blocker comparisons

For non-selective beta-blockers, labetalol appeared to have the least effect on FEV1 whilst propranolol had the greatest falls in FEV1 (figure 19). Compared to control, labetalol caused a mean percentage change in FEV1 of -2.7% (95%CI -9.6 to 4.1, figure 20). In comparison, propranolol caused a mean percentage change in FEV1 of -17.0% (95%CI -21.4 to -12.6, figure 21). Beta2-agonists caused an increase in FEV1 beyond baseline with labetalol and pindolol only.

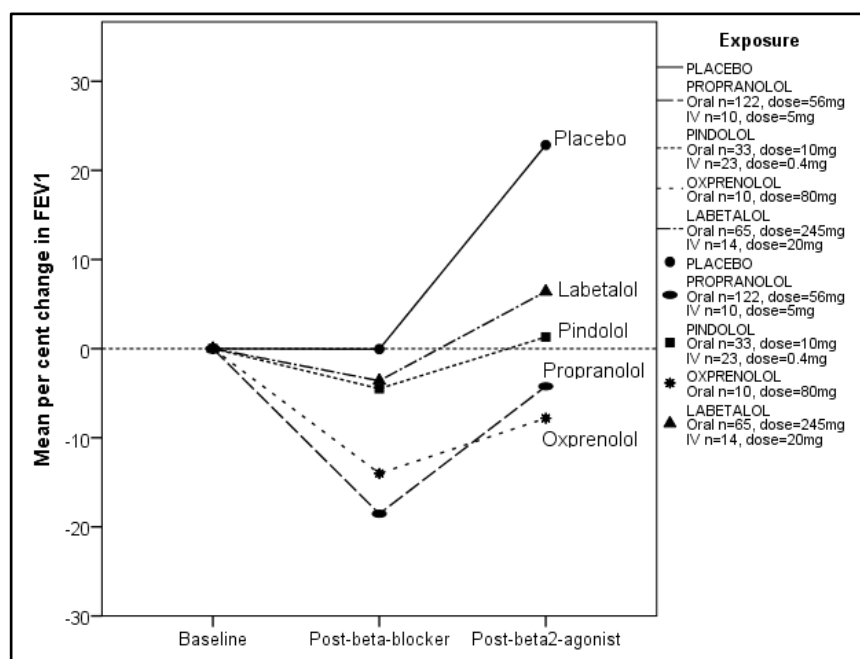


Figure 19. Mean percentage change in FEV1 and response to beta2-agonist relative to baseline following acute non-selective beta-blocker exposure.

*Baseline represented by dotted line. Dose = mean dose; N=number of participants.

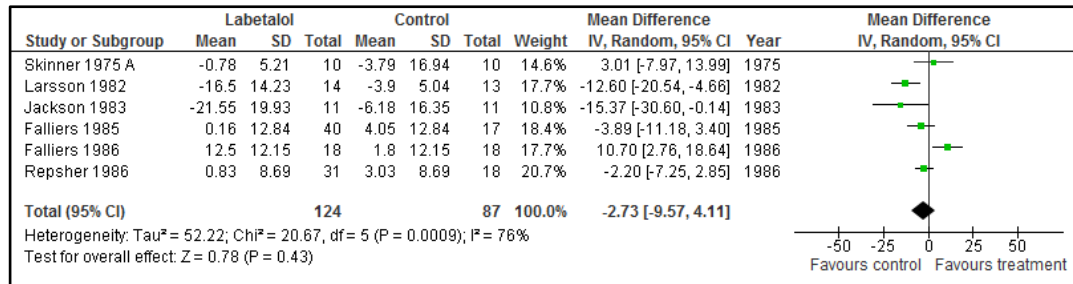


Figure 20. Mean percentage change in FEV1 following acute labetalol exposure.

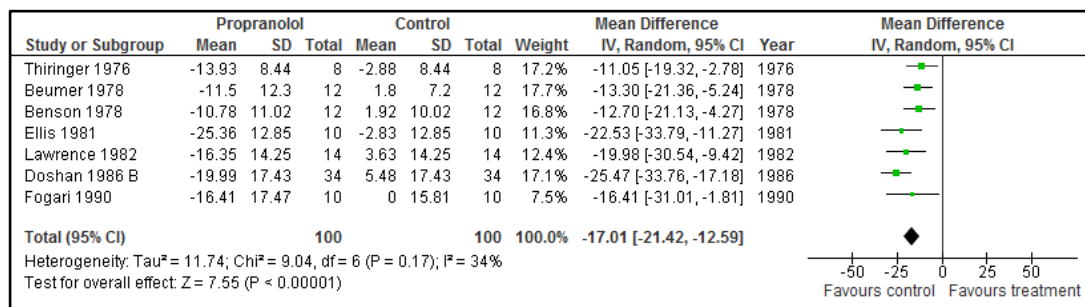


Figure 21. Mean percentage change in FEV1 following acute propranolol exposure.

Sensitivity analysis and risk of bias

Subgroup sensitivity analyses assessed whether mean change in FEV1 varied between studies with unstated vs clearly defined diagnostic criteria for asthma, or varied depending on whether beta2-agonists were withheld prior to testing. These factors had no significant influence on mean fall in FEV1. For selective beta-blockers, mean fall in FEV1 was -6.4% (95% CI -8.3 to -4.5) for studies diagnosing asthma with specific criteria withholding beta2-agonists versus -8.7% (95% CI -12.0 to -5.4) for those which did not. For selective beta-blockers, this sensitivity analysis mainly evaluated the definition of asthma because only 1 study failed to report whether beta2-agonists were withheld prior to testing. For non-selective beta-blockers: mean fall in FEV1 was -8.6% (95% CI -13.7 to -3.5) for studies using explicit criteria for the diagnosis of asthma versus -12.6% (95% CI -21.6 to -3.7) for those which did not. Mean fall in FEV1 was -10.0% (95% CI -15.2 to -4.8) for studies withholding beta2-agonists versus -9.3% (95%

CI -17.9 to -0.7) for those which did not. The final sensitivity analysis consisted of using the minimum and maximum p-value to calculate missing standard deviations as per the methods chapter. The results from this sensitivity analysis were similar to the main analysis. For selective beta-blocker, mean percent change in FEV1 using the minimum imputed p-value was -6.9% (95% CI -8.6 to -5.2) and -7.7% (95% CI -10.1 to -5.4) using the maximum imputed p-value. For non-selective beta-blockers, mean percent change in FEV1 using the minimum imputed p-value was -9.5% (95% CI -13.38 to -5.66) and -11.1% (95% CI -16.1 to -6.2) using the maximum imputed p-value.

For many of the methodological qualities assessed there was an unclear risk of bias as studies did not provide explicit detail to make an informed judgement (figure 22). For studies evaluating mean percentage change in FEV1, funnel plot asymmetry was observed for selective beta-blockers (figure 23). Because funnel plot asymmetry was observed, the Egger test was performed and was statistically significant for selective beta-blockers (p-value=0.005) but not for studies evaluating non-selective beta-blockers (p-value=0.111).

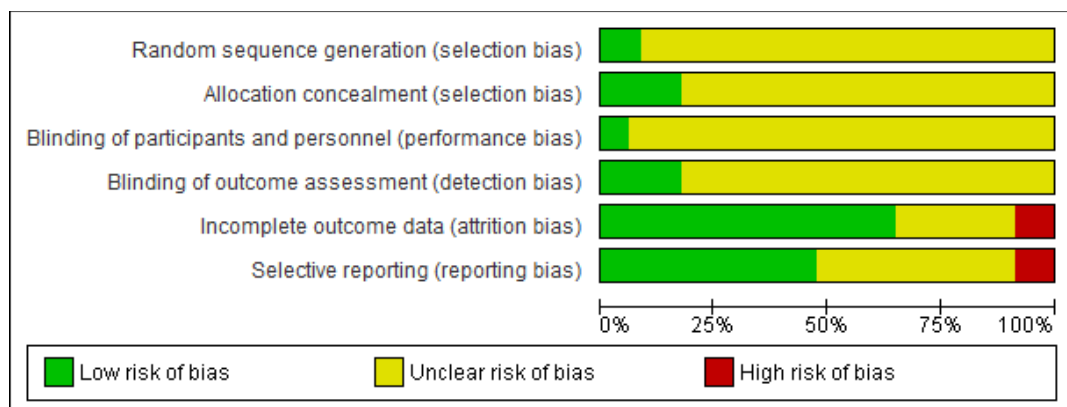


Figure 22. Cochrane collaboration risk of bias tool for included studies in the beta-blocker systematic review.

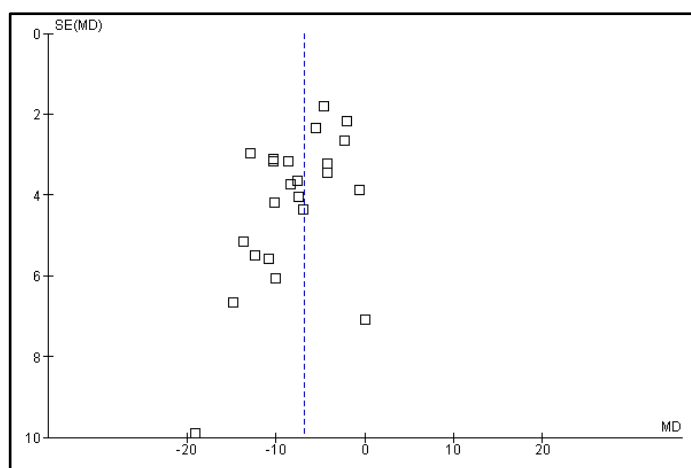


Figure 23. Funnel plot for studies reporting mean percentage change in FEV1 following acute selective beta-blocker exposure.

SE(MD)=standard error of the mean difference.

3.5 Discussion

This meta-analysis used clinical trial data to systematically quantify the degree of bronchoconstriction caused by acute exposure to a variety of beta-blockers. Using data from 25 clinical trials I found that acute selective beta-blocker exposure caused relatively small mean reductions in FEV1 and a non-significant increase in respiratory symptoms compared to placebo. However, selective beta-blockers did cause a statistically significant fall in FEV1 of 20% or greater in 13% of people (number needed to harm approximately one in eight). For both mean fall in FEV1 and respiratory symptoms, findings were similar to the meta-analysis by Salpeter et al. evaluating selective beta-blockers in people with reversible airways disease who included people with COPD demonstrating that including people with COPD in their study did not bias their results (87). Apart from only evaluating selective beta-blockers, this meta-analysis did not evaluate fall in FEV1 of 20% or greater as a distinct outcome which was an important finding from this study. Although the incidence of respiratory symptoms following selective beta-blocker exposure failed to reach statistical significance, this

result in combination with falls in FEV1 of 20% or greater suggest that acute selective beta-blocker exposure is not free from potential harm and that detrimental respiratory effects are likely to occur in a significant minority of susceptible people, even if the majority remain unaffected.

Compared to placebo, the FEV1 response to beta2-agonist therapy was blunted by 10.2% following acute selective beta-blocker exposure. This is in contrast to the meta-analysis by Salpeter et al. which reported a 4.6% increase in response to beta2-agonists following single-dose exposure. An increase in beta2-agonist response following single doses of beta-blocker exposure is not biologically plausible given the pathophysiology. This difference can be explained by the use of different baseline definitions from which FEV1 response to beta2-agonists was calculated between studies. In this analysis, response to beta2-agonists was calculated as the mean percentage change in FEV1 relative to baseline FEV1 whilst in the meta-analysis by Salpeter et al. mean percentage change in FEV1 was calculated using post-exposure FEV1 biasing the results. However, blunting of this magnitude in response to beta2-agonists is possibly of limited clinical significance as pulmonary function typically increased well beyond original baseline FEV1 values.

There is no published meta-analysis examining non-selective beta-blockers that I am aware of. Compared to placebo, acute exposure to non-selective beta-blockers caused a mean reduction in FEV1 of 10.2% and a significant increase in respiratory symptoms affecting 8% of patients (numbers needed to harm approximately one in thirteen). Compared to selective agents, non-selective beta-blockers caused a similar but non-significant proportion of participants to have a fall in FEV1 of 20% or greater (11% and

13% respectively), and blunted FEV1 response to beta2-agonists by a much greater amount (20.0%).

Three recent studies published after the search was completed have further examined response to beta2-agonist therapy in people with asthma exposed to non-selective beta-blockers, none of which would have been eligible for this review. In each of these studies, short-acting beta2-agonists were evaluated in response to experimentally induced bronchoconstriction in patients with beta-blocker exposure, which potentially more closely mimics a real life scenario in which people established on beta-blockers have a fall in FEV1 as a result of infection or some other trigger. In the study by Short et al, a high dose of nebulised beta2-agonist (salbutamol 5mg) completely reversed a 10% fall in FEV1 induced by histamine following acute exposure to oral propranolol (doses ranging from 10 to 20mg) in thirteen steroid treated asthmatics (163). In the study by Hanania et al, nebulised salbutamol (at a dose of 2.5mg) completely reversed the effects of metacholine challenge in 18 steroid naïve mild asthmatics receiving chronic nadolol dosing (mean dose 30mg) (164). A subsequent study evaluated the effect of nebulised salbutamol (5mg) in 18 steroid treated asthmatics receiving chronic exposure to propranolol 80mg once daily after an initial period of dose titration. There was a 2.4% fall in FEV1 among people with chronic propranolol exposure compared to placebo and a mean 5.3% fall in FEV1 when salbutamol was administered following a histamine challenge. Despite these small changes, no significant changes in asthma control questionnaire or quality of life were found (165). In contrast, results from this systematic review evaluate the response to beta2-agonist rescue therapy against falls in FEV1 induced directly by acute exposure to beta-blockers (i.e. at the time of their initiation) thus measuring a different effect.

No eligible studies evaluating topical beta-blocker eye drops were found and it has not been possible to quantify the risk from topical beta-blockers. Two randomized placebo controlled trials were ineligible for this systematic review because people were selected on the basis of prior adverse respiratory effects from topical timolol eye drops. In the study by Friren et al, a single drop of the non-selective beta-blocker timolol caused a mean fall in FEV1 of 14.2% (166). In the other study by Schoene et al, a single drop of the selective beta-blocker betaxolol caused a mean fall in FEV1 of 9.6% (167). I chose not to include patients selected on the basis of prior beta-blocker response in this systematic review as this would likely evaluate exposure in a subgroup of patients at different risk of bronchospasm and these patients are unlikely to be representative of all people with asthma.

Heterogeneity in treatment effect

It was possible to investigate heterogeneity in this systematic review due to the large number of eligible trials. Heterogeneity was present as demonstrated by a significant I^2 test in some analyses and through differences between individual drugs and dose response. The subgroup analysis involving individual beta-blockers suggests that clinically important differences in treatment effect vary within class, particularly in relation to celiprolol and labetalol in which mean changes in FEV1 were not significant. The degree of beta1-adrenoceptor selectivity is known to vary among different selective beta-blockers. In this respect, the beta1:beta2-affinity ratios range from 13.5 for bisoprolol to 4.7 for atenolol and 2.3 for metoprolol (72). This is important as variation in beta1-adrenoceptor selectivity may also contribute to heterogeneity in treatment effect in meta-analyses of clinical trials investigating mortality from beta-blockers in the

perioperative setting (168). Celiprolol is a selective beta-blocker with partial agonist activity shown to have greater beta₁-selectivity than both atenolol and bisoprolol and this greater beta₁-selectivity may explain the non-significant mean change in FEV₁ following acute exposure (169, 170). However, labetalol is a non-selective beta-blocker with alpha-blocking properties and in this instance beta₁-adrenoceptor selectivity cannot be the sole reason for better respiratory tolerance. Although labetalol was associated with only small falls in FEV₁ following acute exposure significant heterogeneity was present and it is not possible to provide sufficient details on symptoms, fall in FEV₁ of 20% or greater and response to beta₂-agonist separately to comprehensively evaluate its safety for patients with pregnancy-induced hypertension and asthma.

The method of administration and dose of short-acting beta₂-agonists used in trials from this systematic review varied. In many studies a standard dose of inhaled salbutamol (200 mcg) was administered following relatively high doses of beta-blockers. It is therefore possible that using higher doses of SABA would have a similar therapeutic effect in terms of response to FEV₁ in people given beta-blockers compared to people without beta-blocker exposure. In addition, change in respiratory function was evaluated using FEV₁ which may be less sensitive at assessing pulmonary function following beta-blockade than other methods such as impulse oscillometry (171).

Strengths and limitations

Although studies in this meta-analysis administered clinically recommended doses of beta-blockers, in many instances these doses would be considered high initiation doses (e.g. atenolol 100mg). In reality, most people with (or without asthma) would initiate

treatment at lower doses. No studies titrated the beta-blocker dose in order to minimise adverse effects, as is conventional practice in the treatment of heart failure. As such, the risk presented in this review may not be representative of beta-blockers initiated at much lower doses which are then titrated upwards and may be better tolerated. In many instances the results in this chapter provide important information on the worst case scenario which could occur with unintended beta-blocker exposure. Beta-blockers were also evaluated in patients with mild to moderate asthma and the changes in lung function and symptoms presented in this chapter may not be applicable to patients with more severe or unstable asthma. Many of the included studies were reported at a time when therapeutic options for the management of asthma were limited and it is uncertain whether this may have influenced the results (e.g. through the availability of inhaled corticosteroids which may reduce risk further). In many instances an unclear risk of bias existed mainly because studies failed to describe in detail aspects of study design upon which an informed judgement could be made. Even with the apparent dose-response relationship and observed differences among individual beta-blockers, the possibility that some heterogeneity may be due to bias cannot be excluded. However, I chose to include only randomised blinded placebo controlled trials which are considered to be the gold standard for clinical research and the best method to prevent bias and confounding.

3.6 Summary

Based on a systematic review of all published clinical trial evidence, acute exposure to beta-blockers causes detrimental changes in lung function in susceptible people with asthma. However, the size of lung function changes and incidence of respiratory symptoms is dependent upon the class of beta-blocker and the dose of administration.

This would imply that beta-blockers should only be initiated in people with asthma where there is a compelling clinical indication to use a beta-blocker, in which case beta-blockers with greater beta1-selectivity are likely to be safer and should be initiated at the smallest possible dose. Given that around one in eight people with asthma in the trials experienced a clinically significant decline in FEV1, observation of initiation would be sensible, particularly where asthma is more severe or has been relatively unstable in the past. This is especially important because response to conventional doses of short-acting beta2-agonists is blunted, particularly by non-selective beta-blockers.

An evaluation of the effects of chronic beta-blocker exposure in asthma was beyond the scope of this systematic review. Observational studies describing the pattern of beta-blocker prescribing among people with asthma and comparing beta-blocker risk using routine health data, including associations with both acute and chronic exposure would provide a useful comparison. The results of these observational studies are reported in chapter 7 and chapter 8. The next chapter will report a systematic review on the prevalence of aspirin-sensitivity in asthma using clinical trials and self-reported history.

Chapter 4: Aspirin-Exacerbated Respiratory Disease: Systematic Review and Meta-Analysis of Prevalence and Mean Provocative Dose of Aspirin

4.1 Introduction

Aspirin triggers exacerbations in susceptible patients with asthma. Although referred to as aspirin-exacerbated respiratory disease (AERD), complete cross-reactivity to other NSAIDs occurs. The prevalence of AERD varies widely among the literature. This uncertainty is surprising because asthma is a highly prevalent disease, whilst aspirin and NSAIDs are drugs which are widely used and the susceptibility of some people with asthma to these drugs has long been recognised. These inconsistencies in prevalence appear to relate to the different methods used to diagnose AERD including heterogeneity in study design and in the dose of aspirin administered.

For example, in a study by McDonald et al., forty two patients with an unknown history of aspirin sensitivity but selected on the basis of having a history of nasal polyps or chronic sinusitis were challenged with a 320mg single dose of aspirin (99). In this study, reactions were considered positive if the forced expiratory volume in 1 second (FEV1) fell by 50% or greater. In contrast, in a study by Spector et al. graded doses of aspirin were administered to various groups of asthmatic patients including those with: no history of AERD with aspirin ingestion in the preceding month; those with no history of AERD without aspirin ingestion in the preceding month; those with uncertain history of AERD; and those with a positive history of aspirin-induced respiratory reactions (172). In this study, a fall in FEV1 of 20% or greater was considered a positive reaction. This heterogeneity means it is difficult to make proper comparisons between studies.

The most widely cited estimate of prevalence of AERD comes from a single systematic review on the topic published in 2004 which reported an overall prevalence of AERD of

21% for adults and 5% for children (97). Although that systematic review synthesised studies using oral provocation challenge tests to determine the prevalence AERD, it included studies with heterogeneity in the threshold of FEV1 used to define a positive reaction and different dosing regimens. It therefore included studies such as those described above by McDonald et al. and Spector et al. potentially biasing the estimate of prevalence. Additionally, several reported inaccuracies in the description of included studies appear in that systematic review. For example, the study by Rachelefsky et al. published in 1975 was described as an open challenge study involving 32 children when it was actually a double-blind placebo controlled study involving 50 children (173). The study by Marquett et al. was described as a randomised double-blind placebo-controlled study when in fact it was a retrospective cohort study and the study by Vally et al. was described as a single-blind placebo-controlled study conducting oral provocation challenges when it actually measured the prevalence of AERD through a survey of self-reported history (174, 175). These discrepancies potentially affect the validity of their results.

The prevalence of AERD in people with asthma can be measured from self-reported history or provocation challenge tests. Self-reported histories rely on a degree of self-awareness of aspirin-induced respiratory symptoms which may not be widespread and surveys may be subject to bias depending upon the population sampled (98).

The gold standard method for diagnosing AERD is typically considered to be the oral provocation challenge test, although its validity may be affected through the introduction of bias if inappropriately conducted, for example due to the absence of: a placebo control; blinding of participants (or personnel); random allocation of exposure;

and inappropriate patient selection. The most commonly established method for conducting oral provocation challenge testing for the diagnosis of AERD uses placebo and exposure to incremental doses of aspirin given in single blind fashion over two consecutive days without random allocation of exposure (176). In this regard placebo testing typically occurs on day one with graded aspirin exposure occurring on day 2. The oral provocation challenge test is then considered positive for a diagnosis of AERD when a fall in FEV1 of 20% or greater occurs following exposure to aspirin but not placebo.

Aspirin is a commonly prescribed drug in adults (93). High dose aspirin ($\geq 300\text{mg}$) is recommended for the management of acute coronary syndrome and low dose aspirin (75 to 100mg) is recommended for secondary prevention of cardiovascular (CVS) events with some international guidelines recommending aspirin for primary prevention (177). Increasing evidence demonstrates that aspirin may also reduce cancer-specific mortality potentially prompting wider use among the general population (178, 179). In order to inform the safe use of aspirin in people with asthma, it is important to accurately determine the prevalence of AERD and the provocative dose of aspirin triggering such reactions.

Although the use of self-reported histories has been criticised for the reasons described above, the degree of inaccuracy in measuring the prevalence of AERD compared to oral provocation challenge testing has not definitively been proven or quantified. The systematic review previously discussed measured the prevalence of AERD using oral provocation challenge test studies with varying risk of bias whilst the prevalence of AERD determined using population based surveys of self-reporting remains uncertain.

In addition, the provocative dose of aspirin triggering such events has never been quantified and may guide clinical decision making.

4.2 Aim

The aim of this chapter was to determine the mean provocative dose of aspirin triggering respiratory reactions in people with AERD and to estimate the prevalence of AERD using studies involving oral provocation challenge testing or self-reported history using selection criteria aimed at minimising bias.

4.3 Methodology

Search strategy and selection criteria

The systematic review was conducted using methodology described in the general methods chapter (chapter 2, page 51). A pre-specified search strategy (appendix 1) was used to search MEDLINE, EMBASE and CENTRAL databases. The PICOS approach used in this chapter is described in table 5. The mean provocative dose of aspirin (MPDA) was calculated for adults or children with confirmed AERD only because this is the population at risk. Although nasal challenge testing is possible, the systematic review was restricted to oral provocation challenge testing from which MPDA could be calculated.

For oral provocation challenge tests (OPCT), studies involving adults and children with asthma with unknown AERD status were included. This population therefore had no prior exposure. Although AERD may be triggered by other NSAIDs, the systematic review was restricted to studies performing oral provocation testing with aspirin only.

Table 5. PICOS approach used in the AERD systematic review.

		OPCT	Population surveys	MPDA[‡]
Population	Included	Adults and children with asthma	Adults and children with asthma	Adults and children with AERD
	Excluded	COPD* and healthy people Known AERD status	COPD* and healthy people	Aspirin-tolerant asthma
Intervention	Included	Oral aspirin exposure	Self-reported history of AERD	Graded aspirin exposure
	Excluded	Other NSAIDs Nasal or bronchial exposure		Other NSAID exposure
Comparator	Included	Placebo Aspirin-tolerant asthma	Not applicable	Placebo
Outcomes	Included	Fall in FEV1 of $\geq 20\%$ Respiratory symptoms	Prevalence of AERD	Fall in FEV1 of $\geq 20\%$
	Excluded	Other measures of airway resistance		
Studies	Included	Blinded placebo-controlled	Cross-sectional studies	

*Chronic obstructive airways disease. [‡]Mean provocative dose of aspirin.

OPCT= oral provocation challenge test. AERD=aspirin-exacerbated respiratory disease.

All included challenge test studies were required to be controlled and blinded in order to avoid any placebo effect. Included studies were required to define a positive challenge test by falls in FEV1 of 20% or greater in order to make results more comparable. I included studies measuring the prevalence of AERD using population based surveys which relied upon a self-reported history of respiratory reactions to aspirin or other NSAIDs among adults or children. In this setting, by definition patients were not required to be unselected on the basis of prior exposure.

Data processing and extraction

Data processing and extraction followed the standard methodology set out in the general methods chapter (chapter 2, page 52).

Data analysis

The MPDA was calculated for people with AERD undergoing OPCTs using inverse-variance weighting to pool mean threshold doses from studies. For studies reporting the dose range only, standard deviations were estimated as described by Hozo et al. (chapter 2, page 57).

To estimate prevalence using OPCT studies, falls in FEV1 of 20% or greater and the incidence of respiratory symptoms were calculated in people with asthma with unknown AERD status and presented as the risk difference (RD). For OPCTs, subgroup analysis was performed evaluating differences between adults and children and whether trials were randomised. These subgroup analyses were chosen specifically because differences between adults and children have previously been reported and because lack

of randomisation may introduce bias. For studies measuring AERD by self-reporting, the prevalence of asthma was estimated by calculating the total number of people with self-reported AERD (numerator) divided by the total number of people with asthma (denominator). Subgroup analysis was then performed according to whether people were surveyed in specialist centres or among the general asthma population.

Heterogeneity among studies was assessed using the I^2 statistic with values of greater than 40% indicating heterogeneity. Meta-analysis was performed using a random-effects method of analysis.

Sensitivity analyses

In addition to the standard sensitivity analyses involving the asthma definition, and whether or not beta2-agonists had been withheld for at least 6 hours (chapter 2, page 63), further sensitivity analysis was performed for MPDA according to whether standard deviations were reported or imputed as described Hozo et al.

4.4 Results

Mean provocative dose of aspirin

A total of 1768 references were screened from the three databases. Of these, 20 studies reported oral provocation challenges with aspirin from which the MPDA could be calculated were included (figure 24). The MPDA was reported for 476 people (mean age 44.6 years, 43.6% male) with doses ranging from 30mg to 1000mg (table 6). For adults, the MPDA was 89.0mg (95% CI 75.8 to 102.1mg). The MPDA for children based upon a single small study was 20.6mg (95% CI 4.9 to 36.3mg).

Prevalence of AERD

A total of 7 oral provocation challenge test studies providing data on fall in FEV1 of 20% or greater in people with asthma and unknown AERD status were included. Three studies provided data on respiratory symptoms whilst 4 studies involved children only (table 6). For the main outcomes of fall in FEV1 of 20% or greater and respiratory symptoms, aspirin was evaluated in 381 adults (mean age 41.2 years, 38.6% male) and 156 children (mean age 13 years, 60% male).

Aspirin caused a fall in FEV1 of 20% or greater in 9.0% of adults (95% CI 6.0 to 12.0%, $p<0.001$) and 11.0% of children (95% CI 5.0 to 17.0%, $p<0.001$) with an overall prevalence of 10.0% (95% CI 7.0 to 12.0%, $p<0.001$, figure 25). Respiratory symptoms occurred in 19% of children (95% CI 10 to 28%, $p<0.001$), but symptoms were not reported in any studies involving adults.

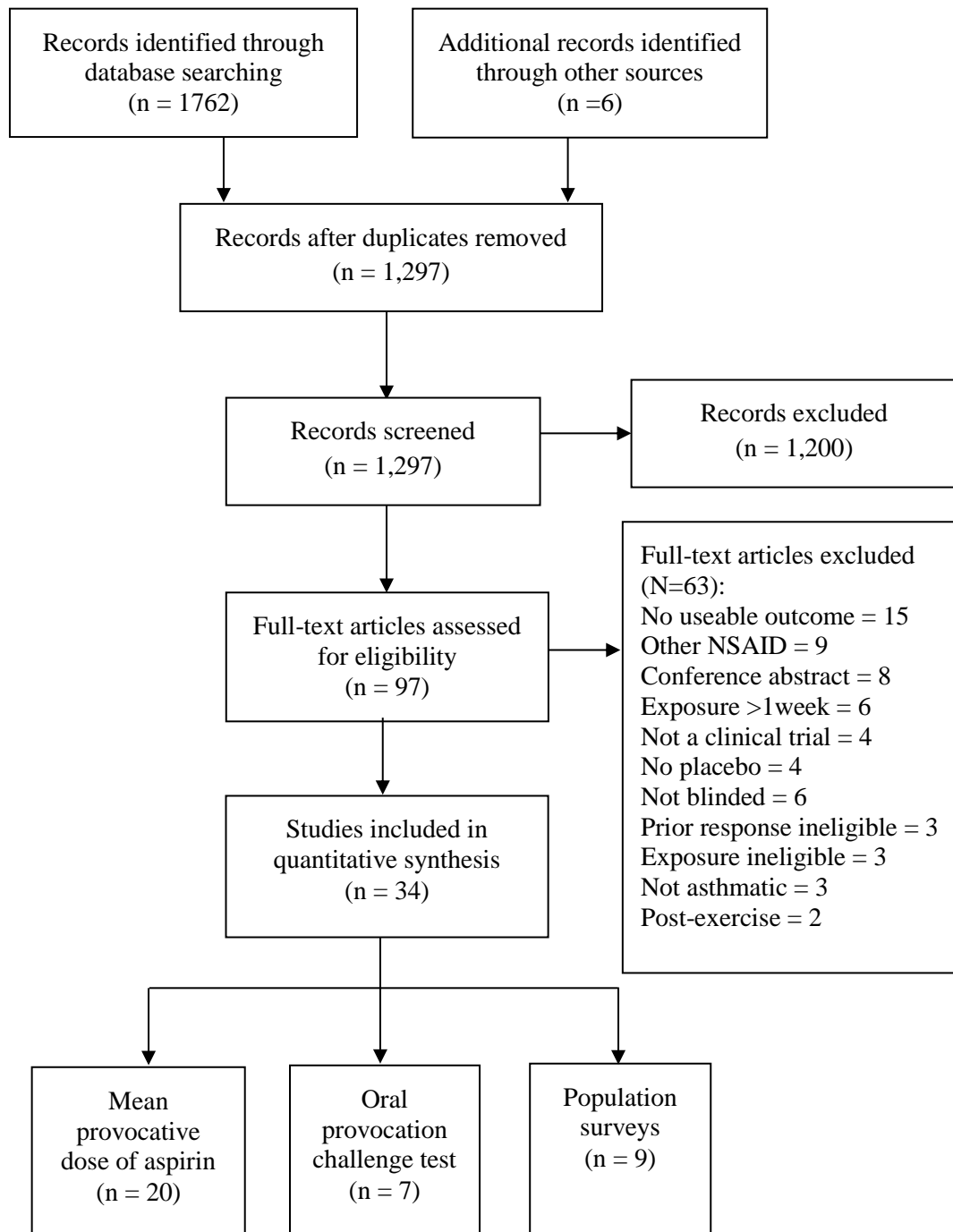


Figure 24. PRISMA flow diagram for study selection in the AERD systematic review.

Table 6. Studies reporting mean provocative dose of aspirin using oral challenge testing.

Study ^(reference)	Patients	Asthma [¥]	SABA ^Ω	Population	MPDA (mg)	
					Dose	SD
MPDA						
Bavbek 2007 ⁽¹⁸⁰⁾	13	Yes	Yes	Adults	163.4	143.9
Berges-Gimeno 2003 ⁽¹⁸¹⁾	38	Yes	No	Adults	58.0	108.1 ^δ
Celejewska-Wójcik 2012 ⁽¹⁸²⁾	8	Yes	Yes	Adults	111.0	108.1 ^δ
Christie 1991 ⁽¹⁸³⁾	6	No	Yes	Adults	31.7	15.9
Falliers 1983 ⁽¹⁸⁴⁾	15	No	No	Adults	142.2	248.6
Israel 1993 ⁽¹⁸⁵⁾	8	Yes	Yes	Adults	90.0	70.0*
Kowalski 1984 ⁽¹⁸⁶⁾	29	Yes	Yes	Adults	140.0	154.3
Kowalski 1985 ⁽¹⁸⁷⁾	11	Yes	Yes	Adults	141.8	173.5
Mastalerz 2000 ⁽¹⁸⁸⁾	17	Yes	Yes	Adults	188.0	197.7
Micheletto 2006 ⁽¹⁸⁹⁾	19	Yes	Yes	Adults	68.3	12.4
Nizankowska 2000 ⁽¹⁷⁶⁾	24	Yes	Yes	Adults	66.1	99.3*
Spector 1979 ⁽¹⁷²⁾	189	Yes	Yes	Adults	119.1	137.3
Stevenson 1984 ⁽¹⁹⁰⁾	25	Yes	No	Adults	364.0	263.3*
Stevenson 2001 ⁽¹⁹¹⁾	60	No	Yes	Adults	61.0	30.0*
Swierczynska 2003 ⁽¹⁹²⁾	15	Yes	No	Adults	103.7	93.0
Szczelkik 2001 ⁽¹⁹³⁾	12	Yes	Yes	Adults	98.3	30.8*
Vedanthan 1977 ⁽¹⁹⁴⁾	52	Yes	Yes	Children	20.6	11.3
Weber 1979 ⁽⁴⁶⁾	12	No	No	Adults	250.0	93.8*
Woessner 2002 ⁽¹⁹⁵⁾	60	Yes	No	Adults	69.0	30.0*
Woessner 2004 ⁽¹⁹⁶⁾	56	Yes	No	Adults	57.0	30.0*

¥ Whether or not studies defined asthma as per sensitivity analyses. MPDA = mean provocative dose of aspirin.

Ω Whether or not studies withheld short-acting beta2-agonists (SABA) for at least 6 hours prior to challenge testing.

SD = standard deviation. *Standard deviations estimated from the range. ^δ Mean standard deviation imputed.

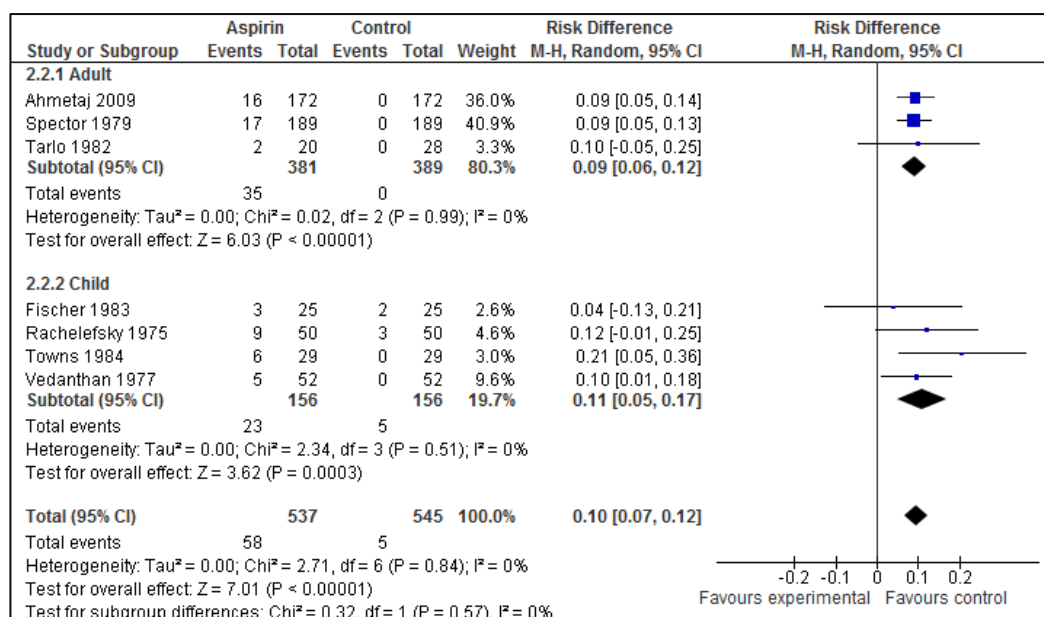


Figure 25. Fall in FEV1 of 20% or greater following oral provocation tests with aspirin.

Table 7. Studies measuring prevalence of aspirin-exacerbated respiratory disease using self-reported histories.

Study	Population	Patients	Prevalence %	Prevalence 95%CI
OPCT studies				
Ahmetaj 2009	Adults	172	9.3	5.8-14.6
Fischer 1983	Children	25	4.0	0.1-19.5
Rachelefsky 1975	Children	50	12.0	5.6-23.8
Spector 1979	Adults	189	9.0	5.7-13.9
Tarlo 1982	Adults	20	10.0	2.8-30.1
Towns 1984	Children	29	20.7	9.9-38.4
Vedanthan 1977	Children	52	9.6	4.2-20.6
Population surveys				
Bavbek 2012	Adults	1344	12.4	10.4-14.7
Eriksson 2014*	Adults	1727	5.1	4.2-6.2
Hedman 1999*	Adults	158	8.8	5.4-14.3
Kasper 2003	Adults	703	4.3	3.0-6.0
Kasper 2009	Adults	582	1.9	1.1-3.4
Mascia 2005	Adults	3307	13.9	12.7-15.1
Moon 2013	Adults	1173	5.8	4.6-7.3
Sabry 2010	Adults	365	12.6	9.6-16.4
Vally 2002*	Adults	644	12.3	10.0-15.0

CI = confidence interval.

There was no significant difference in falls in FEV1 of 20% or greater according to whether or not aspirin was randomly allocated (9% (95% CI 6 to 13%) for randomised vs 10% (95% CI 6 to 14%) for non-randomised studies), although all of the non-randomised studies only involved children. No significant heterogeneity was detected by the I^2 test.

A total of 9 studies involving 10,011 people with asthma (mean age 46.6 years, 63.2% female) provided data on the prevalence of AERD measured using self-reported history (table 7). The overall prevalence of AERD among these studies was 9.6% (95% CI 9.1 to 10.2%). The prevalence of AERD among people sampled from specialist centres was significantly larger than the general asthma population (10.5% (95% CI 9.8 to 11.2%) vs. 6.9% (95% CI 5.9 to 8.0%) respectively, difference 3.6% (95% CI 1.8 to 5.3%)).

Sensitivity analysis and risk of bias

For oral provocation challenge test studies, asthma was defined using explicit best practice criteria described in the general methods chapter in all but one study involving adults only. The prevalence of AERD in the study without an explicit definition of asthma by Ahmetaj et al. was 9% (95% CI 5 to 14%) and was similar to the results of the main analysis. A total of three studies performing oral provocation challenge tests provided no information on whether beta2-agonists were withheld prior to testing but results were similar to those studies which did (prevalence 9% (95% CI 6 to 13%) and 10% (95% CI 6 to 15%) for studies withholding and not withholding beta2-agonists respectively). The MPDA was similar for studies reporting the standard deviation compared to those which were estimated as per the methods section (MPDA 84.0mg for studies reporting the standard deviation vs. 76.6mg for those in which it was estimated).

For many of the methodological qualities assessed risk of bias was either low or unclear whilst a high risk of bias was attributed to the absence of random allocation of aspirin exposure (figure 26). No funnel plot asymmetry was found upon visual inspection of studies measuring the prevalence of AERD using oral provocation challenge tests (figure 27).

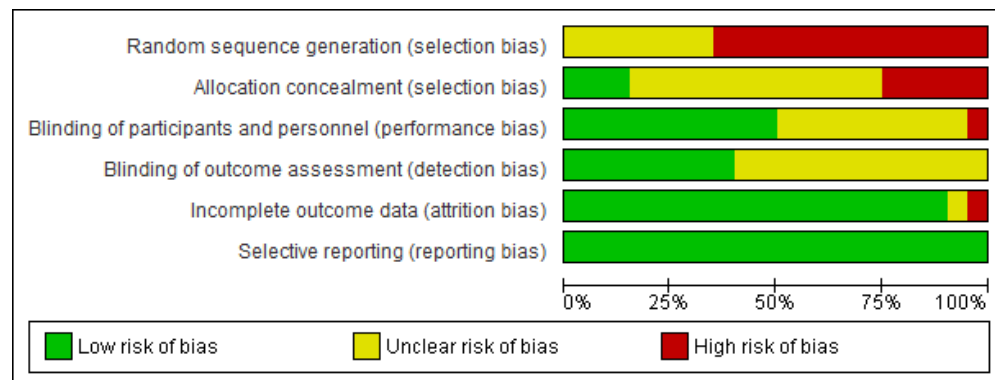


Figure 26. Risk of bias table for included studies performing oral provocation challenge tests.

High risk of bias relates mainly to the non-random administration order of placebo and aspirin.

Comparison with previous evidence synthesis

Table 8 lists the OPCT studies which were excluded from this systematic review on the basis of pre-specified selection criteria but which were included in the systematic review by Jenkins et al. along with the prevalence of AERD from each study. A total of five studies present in the systematic review by Jenkins et al. with an overall prevalence of AERD of 23.4% were excluded by our review because they did not meet the eligibility criteria in terms of FEV1 used to diagnose AERD, no use of blinding or placebo and using a population suspected of having AERD. The overall prevalence of AERD among three studies included in both reviews was 9.6% and the overall prevalence of AERD among new studies (or those previously unavailable to Jenkins et al.) was 10.2%.

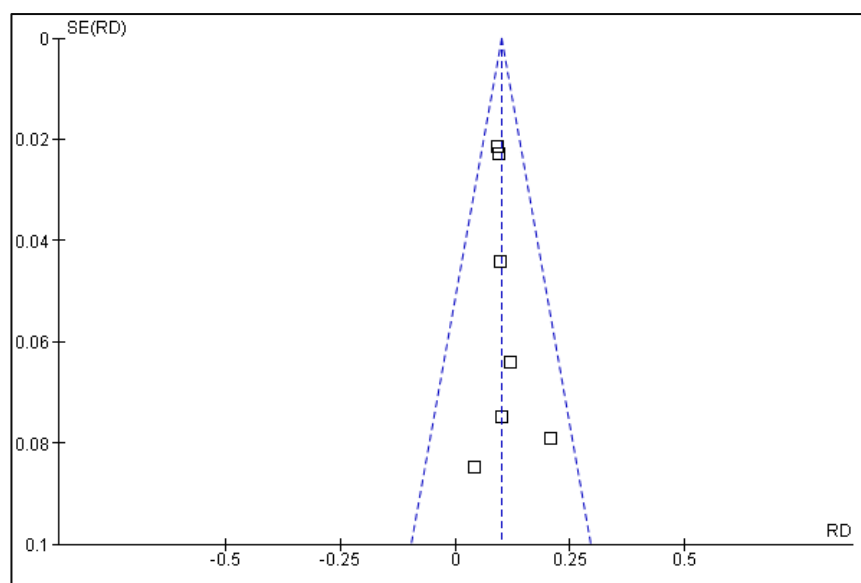


Figure 27. Funnel plot for studies reporting falls in FEV1 of 20% or greater in AERD studies.

SE(RD) = standard error of the risk difference.

Table 8. Prevalence of aspirin-exacerbated respiratory disease among studies included and excluded in the systematic review by Jenkins et al.

Studies	Prevalence (%)	No. Patients
Included		
Rachelefsky 1975	12.0	50
Spector 1979	9.0	189
Vedanthan 1977	10.0	52
Overall	9.6	291
Excluded		
Delaney 1976	19.1	230
Weber 1979	50.0	30
Stevenson 1975	24.6	122
Schuhl 1979	20.7	29
Overall	23.4	411
New*		
Ahmetaj 2009	9.0	172
Fischer 1983	4.0	25
Tarlo 1982	10.0	20
Towns 1984	21.0	29
Overall	10.2	246

*Or previously unavailable to Jenkins et al. (97).

4.5 Discussion

The mean provocative dose of aspirin was around 89 mg. These doses are clinically relevant because guidelines recommending aspirin for the primary or secondary prevention of cardiovascular (CVS) disease advocate doses of 75 to 100mg. Indeed, several large randomised clinical trials are currently underway investigating the safety and efficacy of 100mg aspirin daily as primary prevention in people at increased CVS risk (177).

It was not possible from this study to determine the prevalence of AERD triggered by different clinical doses of aspirin in order to quantify the potential risk reduction in using 75mg of aspirin compared to 100mg. However, individual susceptibility to aspirin varied considerably and potentially not all people with AERD will have adverse respiratory events triggered by low dose aspirin although more people would be expected to be symptomatic with higher doses such as those recommended in acute coronary syndrome (≥ 300 mg). Recommendations on the safe use of aspirin in the management of CVS disease typically consider the net clinical benefit where harms are heavily weighted towards risk of bleeding (gastrointestinal and intracranial). For people with asthma, the risk of adverse respiratory events in people with AERD should also be considered especially if aspirin becomes more widely prescribed as a putative anti-cancer agent.

The prevalence of AERD in asthma was found to be 9% in adults as determined by falls in FEV1 of 20% or greater using blinded, placebo-controlled oral provocation challenge tests and 9.6% as determined using population surveys reliant upon self-reported history. The previous systematic review of oral provocation challenge tests by Jenkins

et al. reported a prevalence of AERD affecting 21% of adults and 5% of children with asthma (97). That review included several oral provocation challenge test studies which were unblinded or uncontrolled potentially biasing the results. The systematic review by Jenkins et al. also included studies with heterogeneity in FEV1 values used to define positive reactions and studies in which some patients underwent oral provocation challenge tests for suspected AERD rather than using a general asthma population with unknown AERD status, potentially causing selection bias leading to the prevalence being overestimated.

The study by Delaney et al. was not included because around half of people had a prior history of aspirin sensitivity (197). The study by Weber et al. was not included because it was an open label study performed in people suspected of having asthma triggered by aspirin (198). The study by Stevenson et al. was not included because of an unclear description of the oral challenge testing procedure performed although it did reference the methodology by McDonald et al implying a similar approach was taken. This study by McDonald et al. selected people on the basis of having a history of nasal polyps or chronic sinusitis, were challenged with a 320mg single dose of aspirin and reactions were considered positive if FEV1 fell by 50% or greater, criteria which would make it ineligible for this systematic review (99). Finally, the study by Schuhl et al. performed provocation challenge tests which were not subject to blinding, were uncontrolled and used changes in peak expiratory flow rather than FEV1 to determine a positive reaction (199).

Strengths and limitations

The estimate for the prevalence of AERD based upon oral provocation challenge testing in this chapter is lower than in the previous systematic review because the approach I took aimed to minimise bias whilst also including additional studies not previously evaluated. These four additional studies had a similar overall prevalence to studies which were included in both systematic reviews. Although the systematic review of oral provocation studies which I undertook was designed to minimise bias, the oral provocation studies in this systematic review may still not truly be representative of the general asthma population as many studies involved people referred to specialist centres for the management of asthma. In which case, a prevalence of 10% may still be an overestimate.

One included study estimating the prevalence of AERD using self-reported history also performed oral provocation challenge testing among a small number of respondents (200). Several people with a positive history of AERD subsequently had negative challenge tests and vice versa suggesting that the diagnosis of AERD by self-reporting can still be unreliable at an individual level. Despite these limitations and previous criticisms around the reliability of studies based upon self-reporting, the prevalence of AERD measured in this way was remarkably similar to that determined by oral provocation studies in our review. This demonstrates some degree of validity in using population surveys of self-reporting to determine the prevalence of AERD at a population level. When the prevalence of AERD measured by self-reporting was stratified by population type, those studies sampling people from the general population had a significantly lower prevalence of AERD compared to people evaluated from specialist centres. A possible explanation for this is that people with AERD appear to

have more severe asthma and be at increased risk of asthma morbidity compared to people with aspirin-tolerant asthma and people with AERD are more likely to be referred to specialist centres (200, 201). In addition, specialist centres may also be better at suspecting and testing for AERD.

The prevalence of AERD among adults and children undergoing oral provocation challenge testing were also similar. Although usually considered to be more commonly a condition of adulthood, aspirin sensitivity has been known to cause severe reactions in children with AERD suggesting that development of chronic rhinosinusitis (a classical feature of AERD) is still an important factor when considering the diagnosis in younger people. In reality though, children are not generally exposed to aspirin due to concerns over Reyes' syndrome and the main safety concern in this population is the prevalence of cross-reactivity to other NSAIDs which occurs in most aspirin-sensitive subjects if sufficient doses are administered (97). Only one randomised blinded placebo-controlled trial has evaluated the prevalence of NSAID sensitivity among children with asthma. This trial evaluated ibuprofen (10mg/kg) in 100 children (mean age 11 years) and reported a prevalence of ibuprofen sensitivity of only 2% (202). This trial excluded children with known ibuprofen sensitivity and included children who had previously used NSAIDs as long as exposure had not occurred within 24 hours of study entry thus potentially underestimating the true prevalence of AERD in patients. In this instance, the most appropriate study population in which to determine an unbiased estimate of ibuprofen sensitivity would have been children without any prior history of aspirin or NSAID exposure. Although our systematic review included oral provocation studies with non-random allocation of aspirin exposure, sensitivity analysis revealed no significant difference when compared suggesting that inclusion of these studies did not

bias the result. In contrast, respiratory symptoms were reported in non-randomised studies involving children only and bias in this setting is perhaps more difficult to assess.

4.6 Summary

On average, AERD was triggered by clinically relevant doses of aspirin suggesting that reasonably large numbers of people with asthma would potentially be at risk of adverse respiratory events associated with aspirin and NSAID exposure. The estimated prevalence of AERD as determined by falls in FEV1 of 20% or greater from blinded, controlled oral challenge tests was 9% in adults and 11% in children. The prevalence of AERD as determined through self-reported history was 9.6% in adults. The prevalence of AERD was higher among people referred to specialist centres. This supports the importance of investigating potential adverse respiratory effects associated with the prescribing of these drugs to people with asthma in the community using electronic primary health care records presented in chapter 9. The next chapter will focus upon quantifying whether selective NSAIDs and COX-2 inhibitors have different risk profiles among people with AERD using a systematic review and meta-analysis of controlled clinical trials.

Chapter 5: Acute Exposure to Selective NSAIDs or COX-2 Inhibitors in People with AERD: Systematic Review and Meta-Analysis of Controlled Clinical Trials

5.1 Introduction

The systematic review reported in chapter 4 estimated the prevalence of aspirin-exacerbated respiratory disease (AERD) among people with asthma from studies performing oral provocation challenge tests and surveys measuring self-reported history. Aspirin and other non-selective NSAIDs cause bronchoconstriction in susceptible people with asthma as a result of inhibiting the COX-1 enzyme which leads to increased levels of cysteinyl leukotrienes (94, 95). The systematic review by Jenkins et al. also measured cross-reactivity to other non-selective NSAIDs in people with aspirin-sensitivity. That review evaluated three studies meeting their inclusion criteria and found that the incidence of cross-reactivity was 98% for ibuprofen (at an oral dose of $\leq 400\text{mg}$), 100% for naproxen (at an oral dose of $\leq 100\text{mg}$) and 93% for diclofenac (at an oral dose of $\leq 40\text{mg}$) (97). Reactions to aspirin and non-selective NSAIDs are thought to occur within several hours of ingestion forming the basis for oral provocation challenge testing. These reactions also commonly trigger upper respiratory symptoms including rhinorrhoea and nasal obstruction which may affect quality of life (172, 190, 203). This has led to recommendations by regulatory agencies that all NSAIDs should be contraindicated in people with AERD which can be found on corresponding summaries of product characteristics. Without routine provocation testing, it is difficult to advise people with asthma on the safe use of non-selective NSAIDs unless they have already exposed themselves to an NSAID or aspirin.

Selective NSAIDs and COX-2 inhibitors act through preferential inhibition of COX-2 over COX-1, potentially leaving the balance between pro-inflammatory and anti-inflammatory mediators unaltered and cysteinyl leukotriene levels unchanged (105). Therefore selective NSAIDs, COX-2 inhibitors, or both would be expected to have a

lower risk of adverse respiratory effects in people with AERD. However, the degree of COX1: COX-2 selectivity for NSAIDs varies between different drugs and selective NSAIDs are less selective than COX-2 inhibitors, especially at higher doses (204). Selective NSAIDs may be an attractive therapeutic option for people with AERD or in those people with asthma with an unknown AERD status who are unwilling to accept the risk from incident exposure when provocation challenge testing is not routinely available. Unlike cross-reactivity to non-selective NSAIDs, a systematic review has never been performed quantifying the degree of cross-reactivity to selective NSAIDs and COX-2 inhibitors in people with AERD.

5.2 Aim

The aim of this chapter was to assess the incidence of adverse respiratory events from clinical trials evaluating acute exposure to selective NSAIDs and COX-2 inhibitors in people with AERD in order to better inform their use.

5.3 Methodology

Search strategy and selection criteria

The systematic review was conducted using methodology described in the general methods chapter (chapter 2, page 51). A pre-specified search strategy (appendix 1) was used to search MEDLINE, EMBASE and CENTRAL databases. The PICOS approach used in this chapter is described in table 9. Only studies evaluating oral selective NSAIDs and COX-2 inhibitors among people with AERD were included because cross-reactivity to non-selective NSAIDs has already been well quantified and selective NSAIDs/COX-2 inhibitors are potentially a useful safe alternative. Only blinded placebo-controlled studies were included to minimise bias.

Table 9. PICOS approach used in the selective NSAID and COX-2 inhibitor systematic review.

Population	Included	Patients with AERD
	Excluded	Patients without AERD, or with COPD* or healthy patients
Intervention	Included	Oral selective NSAID exposure
	Excluded	Topical or nasal exposure
Comparator	Included	Placebo
Outcomes	Included	Respiratory symptoms and falls in FEV1 $\geq 20\%$
	Excluded	Other measures of airway resistance
Studies	Included	Controlled clinical trials in humans
		Single or double-blinded

*Chronic obstructive pulmonary disease

AERD was defined by respiratory reactions to aspirin or other non-selective NSAIDs in people with a history of asthma. For studies which evaluated selective NSAIDs or COX-2 inhibitors in mixed populations experiencing other types of NSAID-intolerant reactions (e.g. cutaneous reactions or angioedema) as well as respiratory reactions, only people with asthma were included in the analysis from the mixed population.

Data processing and extraction

Data processing and extraction followed the standard methodology set out in the general methods chapter (chapter 2, page 52).

Data analysis

Data analysis followed the standard methodology set out in the general methods chapter (chapter 2, page 53). The outcomes of interest were falls in FEV1 of 20% or greater and the incidence of respiratory symptoms presented as the risk difference (RD).

Respiratory symptoms were defined as lower respiratory symptoms (consisting of wheezing, dyspnoea, or cough) and upper respiratory tract symptoms (consisting of

rhinorrhoea or nasal obstruction). This was done because upper respiratory reactions are common in AERD and may still affect quality of life even if lower respiratory reactions are absent. Subgroup analysis was performed evaluating the effect of not withholding leukotriene antagonists prior to oral provocation testing. This is because leukotriene antagonists theoretically may mask reactions from NSAIDs in AERD suggesting they are safe. Subgroup analysis was also performed evaluating whether trials were randomised because lack of randomisation may introduce bias. A fixed-effect method of analysis was used because no statistical heterogeneity was identified using the I^2 test.

Sensitivity analyses

In addition to the standard subgroup sensitivity analyses assessing the definition of asthma and withholding beta2-agonists for at least 6 hours (chapter 2, page 63), further sensitivity analysis was performed evaluating whether diagnosis of AERD was based upon history or as a result of confirmatory challenge testing at the start of the trial.

5.4 Results

The same database search was used as in chapter 3 producing 1768 references from which 14 trials were included (figure 28). All 14 included trials provided data on lower respiratory tract symptoms, 12 provided data on falls in FEV1 of 20% or greater and 9 provided data on upper respiratory tract symptoms. A total of 485 oral selective NSAID or COX-2 inhibitor acute exposures were evaluated in 426 adult patients with AERD (mean age, 46 years; 38% male). Celecoxib and rofecoxib were the most commonly evaluated COX-2 inhibitors, and meloxicam was the most commonly evaluated selective NSAID. All studies evaluated between one and four single-dose exposures performed over consecutive days.

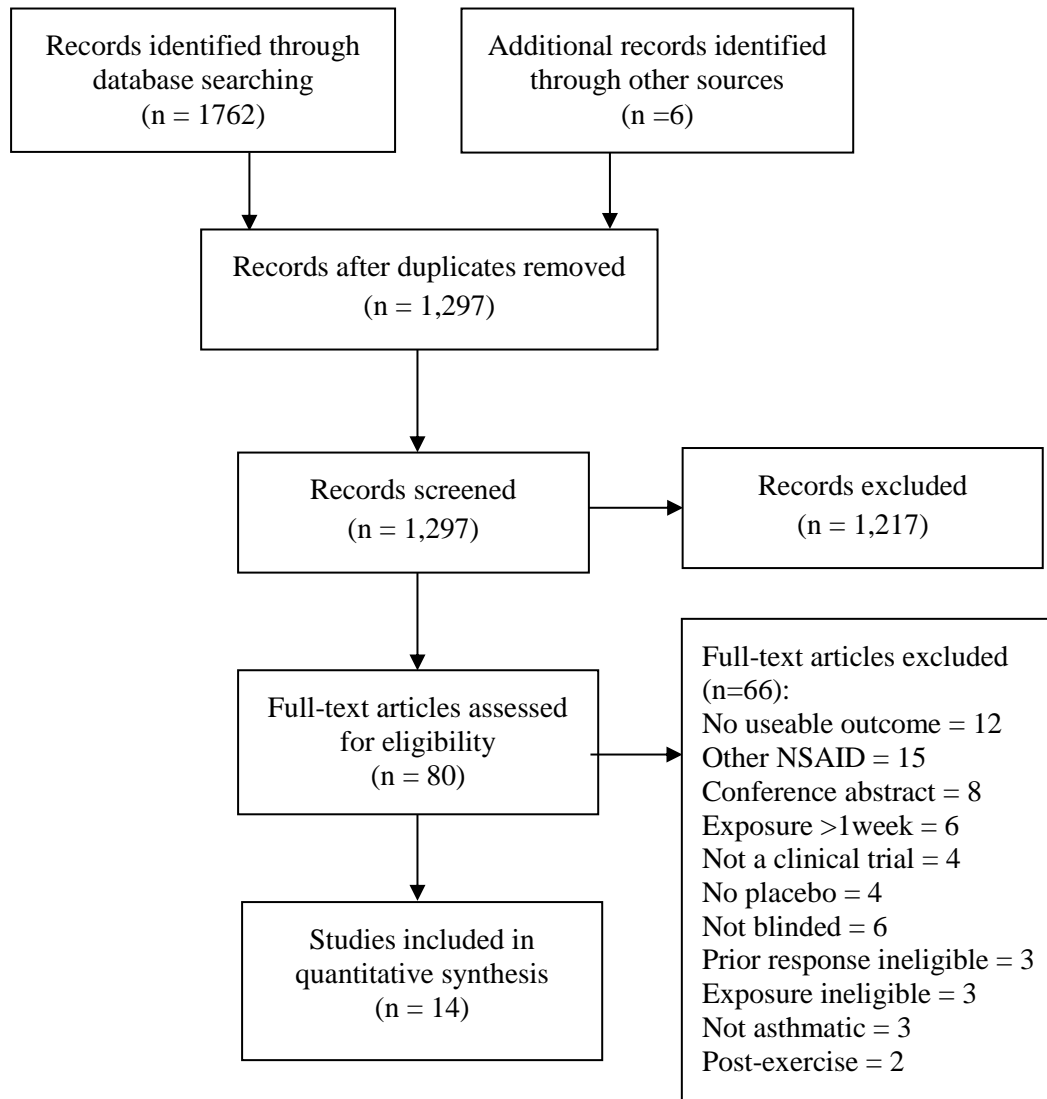


Figure 28. PRISMA flow diagram for study selection in the selective NSAID and COX-2 inhibitor systematic review.

Characteristics of included studies are summarized in table 10. Three trials evaluated selective NSAIDs whilst twelve trials evaluated COX-2 inhibitors. Asthma was defined as per the methods chapter (chapter 2, page 61) in 2 trials evaluating selective NSAIDs and 7 trials evaluating COX-2 inhibitors. Short-active beta2-agonists were withheld at least 6 hours prior to testing in 1 trial evaluating selective NSAIDs and 4 trials evaluating COX-2 inhibitors. Leukotriene receptor antagonists were withheld in 1 trial evaluating selective NSAIDs and 4 trials evaluating COX-2 inhibitors. For selective NSAIDs: the dose of meloxicam evaluated ranged from 7.5mg to 15mg; the dose of nimesulide evaluated was 100mg; and the dose of nabumetone evaluated ranged from 1000mg to 2000mg. For COX-2 inhibitors: the dose of rofecoxib evaluated ranged from 25mg to 50mg; the dose of celecoxib ranged from 200mg to 400mg; and the dose of etoricoxib ranged from 60mg to 120mg.

Challenge testing with COX-2 inhibitors

Among people with AERD, no significant difference was found in falls in FEV1 of 20% or greater following placebo-controlled oral challenge testing with COX-2 inhibitors (RD 0.00 (95% CI -0.02 to 0.02) p=0.77, figure 29). Among people with AERD, no significant difference was found in the incidence of lower respiratory symptoms (RD -0.01 (95% CI -0.03 to 0.01) p=0.57, figure 30) and upper respiratory symptoms (RD -0.01 (95% CI -0.04 to 0.02) p=0.42, figure 31) following placebo-controlled oral challenge testing with COX-2 inhibitors.

Table 10. Characteristics of included studies in the selective NSAID and COX-2 inhibitor systematic review.

Study ^(reference)	Design	Patients^a	Asthma^b	SABA^c	LKT^d	Selective NSAID or COX2 inhibitor
Bavbek 2004 ¹³	NR	31	Yes	No	No	Meloxicam, nimesulide, rofecoxib*
Bavbek 2007 ¹⁴	NR	13	Yes	Yes	No	Meloxicam
El Miedany 2006 ¹⁷	NR	77	Yes	Yes	No	Etoricoxib*
Gylfors 2003 ²⁰	R	33	No	Yes	Yes	Celecoxib*
Martin-Garcia 2002 ²¹	NR	40	No	No	Yes	Rofecoxib*
Martin-Garcia 2003 ²²	NR	33	No	No	Yes	Celecoxib*
Micheletto 2006 ²³	NR	19	Yes	Yes	No	Rofecoxib*
Prieto 2007 ²⁴	NR	29	No	No	Yes	Nabumetone, meloxicam
Stevenson 2001 ²⁷	R	32	No	No	No	Rofecoxib*
Szczelkik 2001 ²⁸	NR	12	Yes	Yes	No	Rofecoxib*
Valero 2002* ³¹	NR	43	No	No	No	Rofecoxib*
Woessner 2002 ³²	NR	25	Yes	No	No	Celecoxib*
Woessner 2004 ³³	NR	22	Yes	No	No	Rofecoxib*
Yoshida 2000* ^{δ 34}	R	17	Yes	No	Yes	Celecoxib*

- a. Only patients with AERD selected from included studies.
- b. Whether or not studies defined asthma as per the general methods chapter (chapter 2, page 61).
- c. Whether or not studies withheld short-acting beta2-agonists (SABA) for at least 6 hours as per the general methods chapter (chapter 2, page 61).
- d. Whether or not studies withheld leukotriene antagonists.

*COX-2 inhibitors (remaining unmarked drugs are classed as selective NSAIDs).

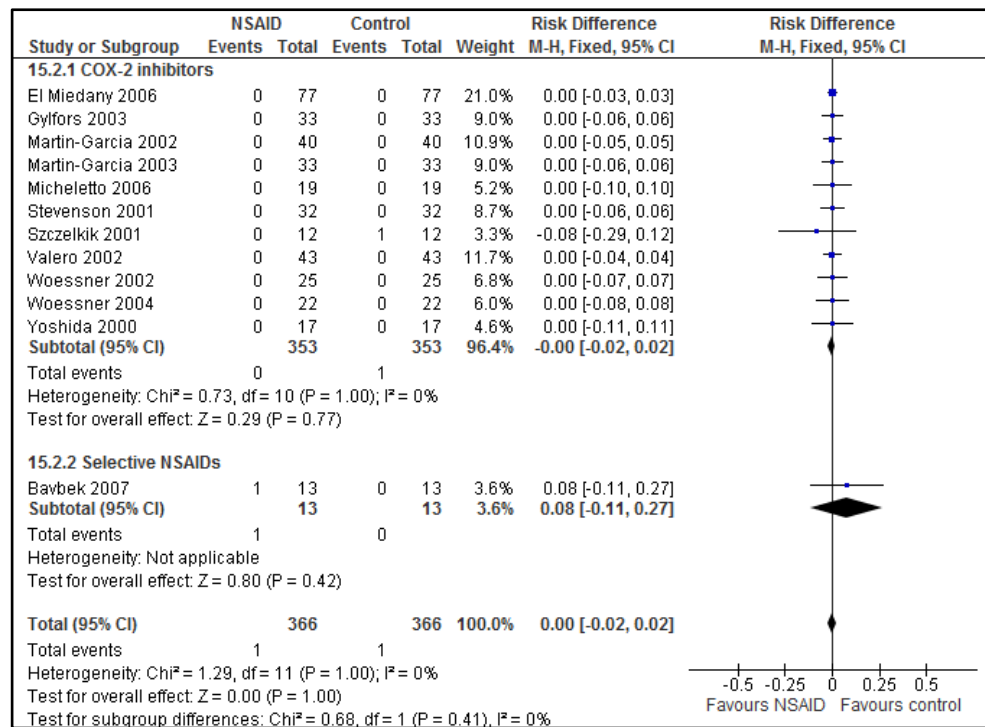


Figure 29. Fall in FEV1 of 20% or greater following acute selective NSAID or COX-2 exposure in patients with aspirin-exacerbated respiratory disease.

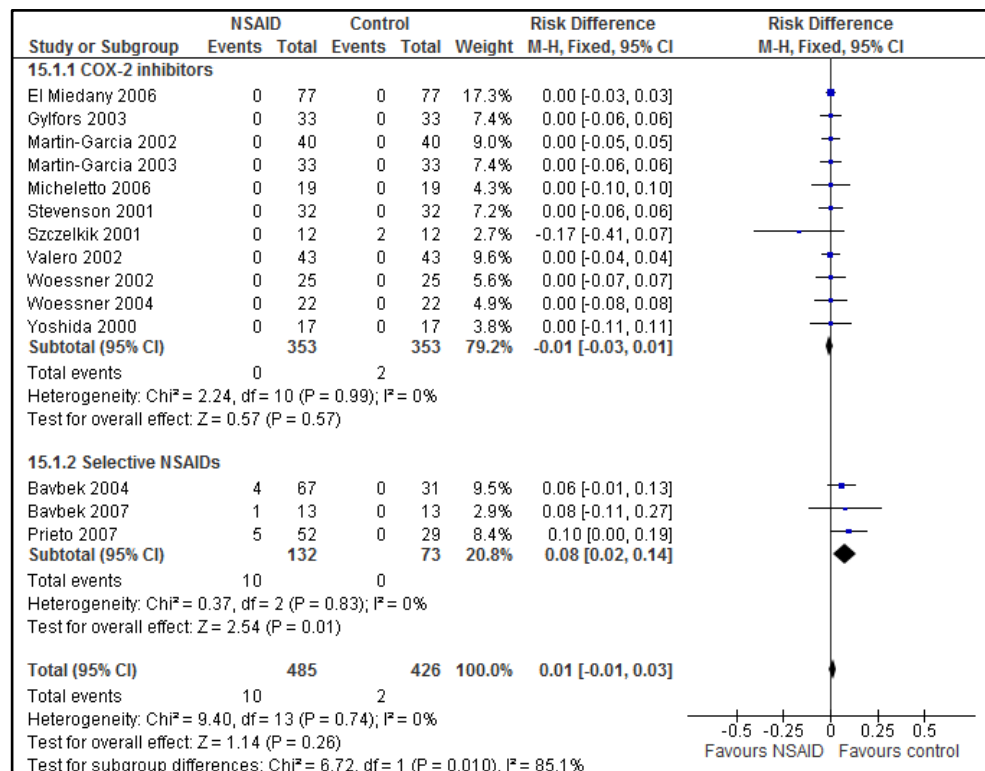


Figure 30. Lower respiratory symptoms following acute selective NSAID or COX-2 inhibitor exposure in patients with aspirin-exacerbated respiratory disease.

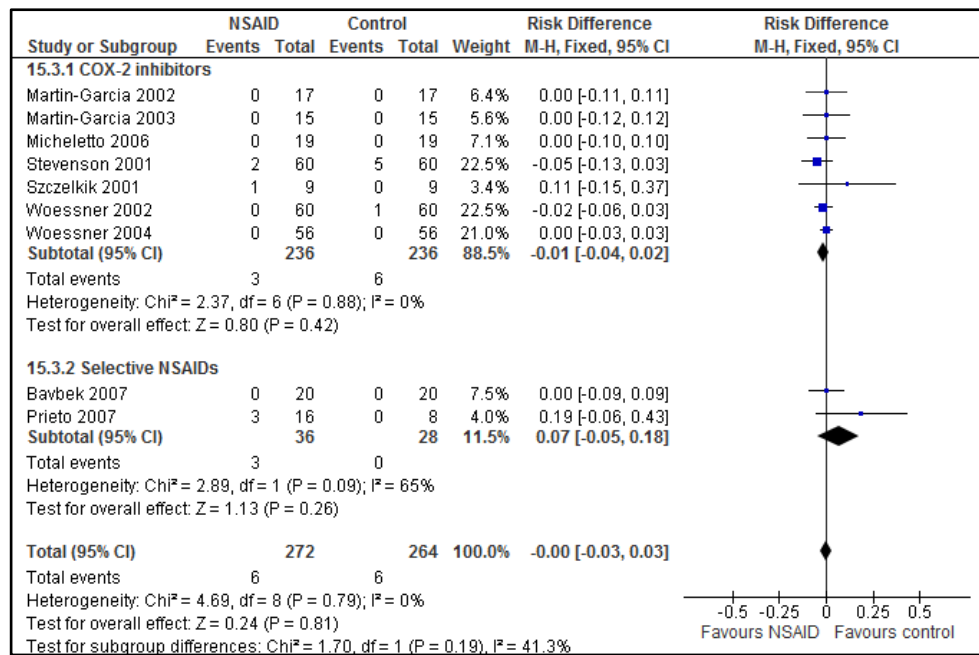


Figure 31. Upper respiratory symptoms following acute selective NSAID or COX-2 exposure in patients with aspirin-exacerbated respiratory disease.

Selective NSAIDs

Among people with AERD, placebo-controlled oral challenge testing with selective NSAIDs caused a significant increase in lower respiratory symptoms (RD 0.08 (95% CI 0.02 to 0.14), $p=0.01$) which equated to a number needed to treat of 13 to cause lower respiratory symptoms in 1 person with AERD. Effect sizes for falls in FEV1 of 20% or greater (RD 0.08 (95% CI -0.11 to 0.27), $p=0.77$) and nasal symptoms (RD 0.07 (95% CI -0.05 to 0.18), $p=0.26$) were similar in size but were not statistically significant (figures 29 to 31).

Subgroup analyses

Leukotriene antagonists. Among people with AERD, leukotriene antagonist exposure had no significant impact on effect estimates for falls in FEV1 of 20% or greater (RD 0.00 (95% CI -0.02 to 0.02) for studies not withholding leukotriene antagonists versus 0.00 (95% CI -0.03 to 0.03) for those which did), lower respiratory symptoms (RD 0.02

(95% CI -0.01 to 0.06) for studies not withholding leukotriene antagonists versus 0.01 (95% CI -0.02 to 0.03) for those which did) or upper respiratory tract symptoms (RD 0.05 (95% CI -0.05 to 0.14) for studies not withholding leukotriene antagonists versus -0.01 (95% CI -0.05 to 0.02) for those which did).

Random allocation of exposure. Among people with AERD, random allocation of exposure had no significant impact on falls in FEV1 of 20% or greater (RD 0.00 (95% CI -0.02 to 0.02) for both randomised and non-randomised studies), lower respiratory tract symptoms (RD 0.01 (95% CI -0.01 to 0.03) for non-randomised studies versus 0.00 (95% CI -0.02 to 0.02) for randomised) or upper respiratory tract symptoms (RD 0.00 (95% CI -0.03 to 0.02) for non-randomised studies versus -0.05 (95% CI -0.13 to 0.03) for randomised).

Sensitivity analyses and risk of bias

The definition of asthma as per the general methods chapter appeared to have no significant influence on the risk difference for falls in FEV1 of 20% or greater (RD 0.00 (95% CI -0.03 to 0.03) for studies which met this definition versus 0.00 (95% CI -0.02 to 0.02) for those which did not), lower respiratory tract symptoms (RD 0.01 (95% CI -0.02 to 0.04) for studies which met this definition versus 0.02 (95% CI -0.01 to 0.04) for those which did not) or upper respiratory tract symptoms (RD 0.00 (95% CI -0.03 to 0.03) for studies which met this definition versus -0.01 (95% CI -0.07 to 0.05) for those which did not).

Withholding SABA for at least 6 hours prior to oral challenge testing appeared to have no significant influence on the risk difference for falls in FEV1 of 20% or greater (RD 0.00 (95% CI -0.03 to 0.03) for studies which withheld SABA versus 0.00 (95% CI

-0.02 to 0.02) for those which did not), lower respiratory tract symptoms (RD -0.01 (95% CI -0.04 to 0.03) for studies which SABA versus 0.02 (95% CI -0.00 to 0.03) for those which did not) or upper respiratory tract symptoms (RD 0.02 (95% CI -0.06 to 0.10) for studies which withheld SABA versus -0.01 (95% CI -0.04 to 0.02) for those which did not).

The definition of AERD determined by history of testing or by oral provocation testing at the beginning of the trial appeared to have no significant influence on the risk difference for falls in FEV1 of 20% or greater (RD 0.00 (95% CI -0.02 to 0.02) for studies which relied upon prior history of testing versus 0.00 (95% CI -0.03 to 0.03) for those which performed oral provocation testing at the beginning of the trial), lower respiratory tract symptoms (RD 0.01 (95% CI -0.01 to 0.03) for studies which relied upon prior history of testing versus 0.01 (95% CI -0.02 to 0.05) for those which performed oral provocation testing at the beginning of the trial) or upper respiratory tract symptoms (RD 0.00 (95% CI -0.09 to 0.09) for studies which relied upon prior history of testing versus 0.00 (95% CI -0.04 to 0.03) for those which performed oral provocation testing at the beginning of the trial).

No significant heterogeneity was found using the I^2 statistic. For the methodological qualities assessed risk of bias was either low or unclear when studies failed to provide explicit detail from which to make an informed judgement. A high risk of bias was detected related to the lack of random allocation of exposure in some studies which did not appear to influence the effect estimates when the above subgroup analysis was performed (figure 32). No funnel plot asymmetry was observed to suggest publication bias (figure 33).

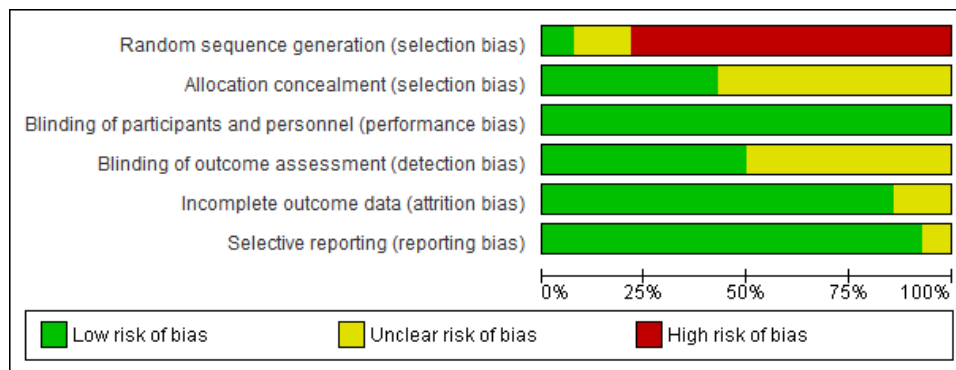


Figure 32. Risk of bias table for included studies in the selective NSAID and COX-2 inhibitor systematic review.

High risk of bias mainly relates to non-random administration order of placebo and NSAID.

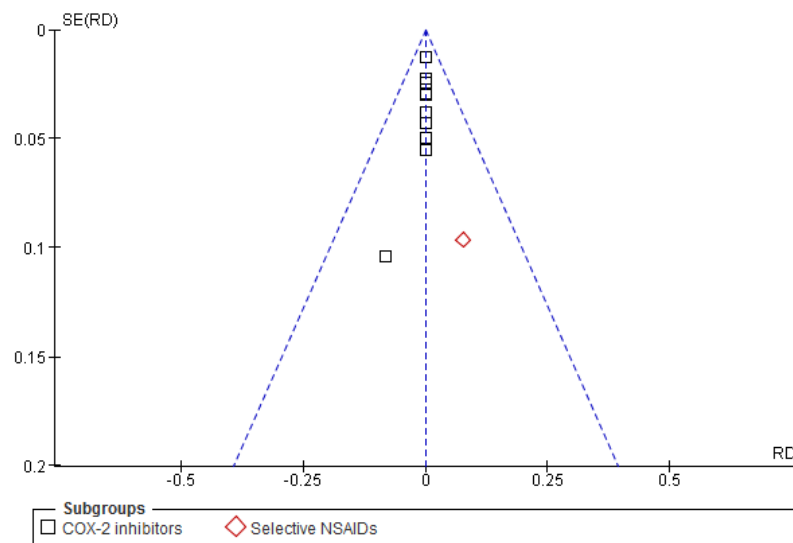


Figure 33. Funnel plot for all studies reporting falls in FEV1 of 20% or greater following oral selective NSAIDs and COX-2 inhibitors.

SE(RD) = standard error of the risk difference.

5.5 Discussion

In this meta-analysis, COX-2 inhibitors did not cause any significant adverse respiratory effects compared to placebo in people with AERD. In contrast a small but statistically significant risk of lower respiratory tract reactions occurred with selective NSAIDs in approximately 1 in 13 patients with AERD. Assuming a prevalence of AERD of around 10%, this would equate to selective NSAIDs causing lower respiratory symptoms in approximately 0.8% of the general asthmatic population, whereas COX-2 inhibitors appear safe to use.

Compared to non-selective NSAIDs, selective NSAIDs evaluated in this chapter have at least 10-fold more selectivity for COX-2 than COX-1. Although COX-2 inhibitors are generally considered to be more than 100 times more selective for COX-2 in human subjects celecoxib has been shown in one study to have a COX-2/COX-1 selectivity ratio similar to meloxicam and nimesulide as determined using a human whole blood assay (205). However, this is in contrast to data derived using recombinant human COX-1 and COX-2 where celecoxib was between 155- and 3,200-fold more selective for COX-2 than COX-1 (206).

In people with AERD, cysteinyl leukotriene levels typically increase during NSAID-induced reactions, and theoretically may be attenuated by exposure to leukotriene antagonists. As such, failure to discontinue such medications at the time of oral challenge testing could potentially mask or underestimate the true risk from selective NSAID or COX-2 inhibitor exposure. This study demonstrated that COX-2 inhibitors appear safe even when exposure to leukotriene receptor antagonist was withheld.

Strengths and limitations

The systematic review reported in this chapter is the largest evaluation of clinical trial evidence on the safety of selective NSAIDs and COX-2 inhibitors in people with AERD. Only blinded placebo-controlled studies were included in order to minimise bias. Although not all studies randomly allocated NSAID exposure as part of their challenge test procedures (potentially introducing bias), subgroup analysis between randomised and non-randomised studies led to the same conclusions. The studies included in this systematic review predominantly evaluated selective NSAIDs or COX-2 inhibitors in people with AERD who had stable, mild to moderate asthma. As such the results from this meta-analysis may not be applicable to patients with unstable asthma or in those who have experienced severe life-threatening reactions requiring intubation following aspirin or NSAID exposure (207). In this regard, subclinical effects are more likely to become evident in people with poorly controlled asthma when only small changes in levels of cysteinyl leukotrienes may precipitate bronchospasm. Therefore it would be safest for people to commence these agents for the first time following optimisation of their asthma.

This analysis was restricted to include only people with asthma who had documented aspirin or NSAID respiratory intolerance. Therefore these results may not be applicable to people suffering other types of NSAID-induced reactions including anaphylaxis, angioedema or cutaneous reactions. Although anaphylactic reactions to COX-2 inhibitors have been reported, these events are rare and possibly distinct to isolated respiratory or nasal reactions commonly encountered by AERD patients (208). In a similar fashion, the occurrence of cutaneous reactions with selective NSAIDs or COX-2 inhibitors in people with AERD has not been evaluated although cross-reactivity with

these agents is believed to be low. This systematic review evaluated moderate doses of selective-NSAIDs or COX-2 inhibitors administered during oral challenge testing and the possibility of reactions occurring following acute high-dose exposure cannot be excluded since selectivity is at least partly dose dependent for some drugs. As such, safe initiation of COX-2 inhibitors in people with AERD is initially likely to involve a low dose with gradual dose titration.

5.6 Summary

According to the available clinical trial evidence, COX-2 inhibitors appear safe to use in people with asthma and AERD whilst selective NSAIDs cause respiratory symptoms in around one in 13 people. The use of COX-2 inhibitors could therefore provide a safe and effective means to anti-inflammatory and analgesic treatment in people with asthma who have true AERD or in those people unwilling to accept the potential risk from non-selective NSAID exposure when oral challenge tests are not routinely available. As with many clinical trials however, this evidence comes from a selected population and generalising these results to all people with asthma is difficult especially if adverse respiratory effects are rare. For this reason, there is still a need to evaluate risk from NSAIDs prescribed to a large general population with asthma which could be achieved through the analysis of routine health data to ensure the results have external validity and are generalizable. The results of these analyses are reported in chapter 9. The next chapter will define the clinical practice research datalink (CPRD) asthma cohort and measure the incidence of asthma events and prevalence of beta-blocker and NSAID prescribing over a twelve year period. This cohort will form the basis for subsequent observational studies reported in chapters 7 to 9.

Chapter 6: Clinical Practice Research Datalink Cohort, Incidence of Asthma Events, and Drug Utilisation Studies

6.1 Introduction

The electronic primary care data used in this thesis comes from CPRD which contains electronic medical records from over 680 UK general practices, with approximately 50% of English CPRD practices additionally linked to the HES database of hospitalisation. Measures of disease occurrence calculated using CPRD data are considered broadly similar to other UK population-based sources. In a study by Booth et al., smoking prevalence estimates for adults over 30 years of age were compared in CPRD and the Health Survey for England between 2007 and 2011, and differences in current and non-smoking estimates occurred in <1% of people (209). In contrast outcome events may be underestimated using CPRD general practice data alone. In a study by Herrett et al., although risk factors had a similar prevalence among people identified in CPRD, HES and other registry sources (such as ONS and the Myocardial Ischaemia National Audit Project, MINAP), relying solely on CPRD underestimated the incidence of acute myocardial infarction by around 25% compared to an approach using linked health records (210). This highlights the importance of using linked healthcare data to avoid biased estimates.

The pharmacoepidemiological studies in this thesis use a cohort of people with active asthma with cohort entry defined by both Read Coding for asthma and prescriptions for asthma medication. The validity of these studies relies in part on accurate outcome ascertainment. One way of checking this is to compare the incidence of outcomes using linked healthcare data in CPRD with national statistics. Measuring the incidence of asthma morbidity and mortality will also allow a better appreciation of the attributable risk associated with the exposures of interest. In the context of this thesis, identifying significant risk factors for asthma exacerbations using linked healthcare data from

CPRD will guide the choice of confounders used for statistical adjustment in subsequent analysis. Finally, understanding patterns of drug utilisation are an important part of pharmacovigilance by providing a better appreciation of the population at risk and how generalizable these results may be to real life clinical practice.

6.2 Aim

The aim of this chapter was to provide background to subsequent chapters by describing the CPRD active asthma cohort, and in this cohort:

1. Calculating incidence rates for asthma morbidity and mortality
2. Identifying risk factors for asthma events and potential confounders
3. Examining beta-blockers and NSAID drug utilisation.

6.3 CPRD Cohort

6.3.1 CPRD cohort - methodology

The CPRD active asthma cohort is described in chapter 2 (page 66). In summary, active asthma was defined by Read Codes for asthma (appendix 2) recorded in the patient's electronic medical record and by prescriptions for asthma medication. The cohort consisted of people aged ≥ 18 present in CPRD from 1 January 2000 to 31 December 2011. Subjects were eligible for cohort entry if they were permanently registered with a general practice for at least one year, were defined by CPRD as being acceptable for use in research, had a Read Code for asthma recorded ever, and were issued two or more prescriptions for asthma medications during their period of registration. An open cohort design was used and cohort entry was defined as the date of the first asthma medication occurring on or after: 1st January 2000; the patient's 18th birthday; or before the patient's 80th birthday. Asthma medications were defined as: inhaled short-acting

beta2-agonists (SABA); inhaled corticosteroids (ICS); inhaled long-acting beta2-agonists (LABA); oral leukotriene antagonists; and oral methylxanthines. Prescriptions for asthma medication were included in the definition to identify patients with active asthma during follow-up. All patients in the cohort were followed up until the first of: an asthma event; deregistration from the practice; one year following the last asthma medication prescription; or end of the study period (31 December 2011). Patients recorded with the following at any point in their electronic medical record or Hospital Episodes Statistics (HES) database were excluded from the cohort: chronic obstructive pulmonary disease (COPD); restrictive lung diseases; and bronchiectasis. Patients prescribed immunosuppressant therapy or with a record of polymyalgia rheumatica were excluded. Characteristics of the active asthma cohort were calculated using means (standard deviation, SD) for continuous variables and numbers (percentage, %) for categorical variables.

6.3.2 CPRD cohort - results

Figure 34 shows how the active asthma cohort was defined by the application of these criteria. A total of 573276 potentially eligible adult patients with a Read Code for asthma and two or more prescriptions for asthma medications during the period of follow-up (active asthma) were identified from CPRD. Of these, 84259 patients (14.7%) were excluded because of comorbidity (COPD, bronchiectasis or restrictive lung disease), 4873 patients (0.9%) were excluded because of immunosuppressant use and 202190 patients (35.3%) were excluded because they were not linked to the HES database of hospitalisation. Characteristics of the active asthma cohort are shown in table 11. The active asthma cohort consisted of 281954 eligible adult patients with mean follow up of 3.0 years per patient

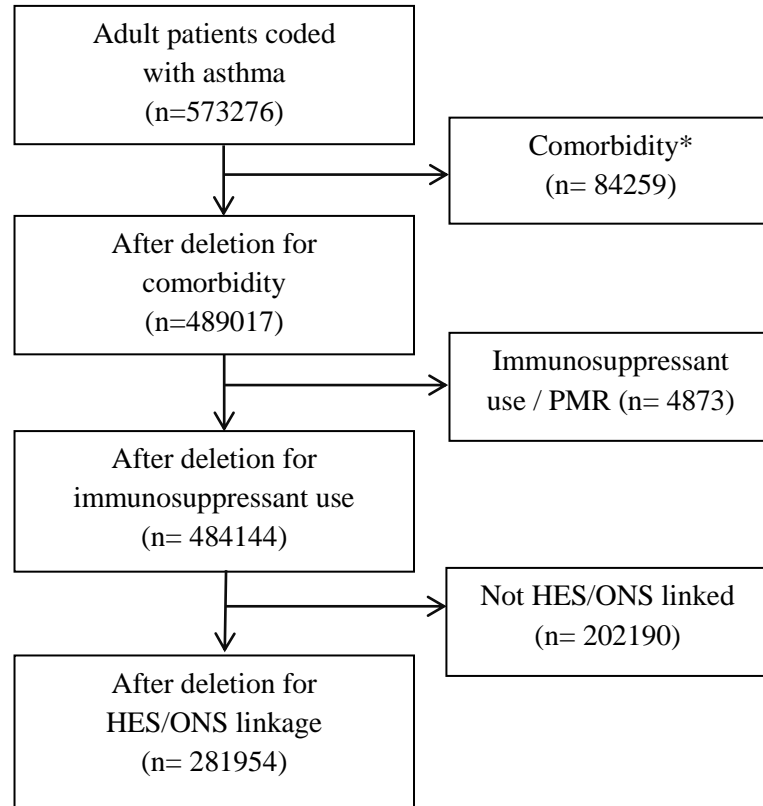


Figure 34. Flow diagram showing derivation of the active asthma cohort.

Table 11. Baseline patient characteristics for the active asthma cohort.

Characteristic	No. patients
Mean years of follow up (SD)	3.0 (3.3)
Mean age at baseline (SD)	38.5 (16.1)
Baseline age category (%)	
▪ 18-29	98882 (35.1)
▪ 30-39	65092 (23.1)
▪ 40-49	47231 (16.8)
▪ 50-59	33016 (11.7)
▪ 60-69	23698 (8.4)
▪ ≥70	14035 (5.0)
Gender (%)	
▪ Male	119008 (42.2)
▪ Female	162946 (57.8)
Smoking Status (%)	
▪ Current	61730 (21.9)
▪ Ex	64347 (22.8)
▪ Never	128088 (45.4)
▪ Missing	27789 (9.1)
Previous hospitalisation* (%)	7497 (2.7)
Mean BMI (SD)	26.2 (7.8)

*Ever been hospitalised for asthma at cohort entry

Mean BMI based on 222589 patients (79.0%) with baseline data.

The mean age at cohort entry was 38.5 years and there were more women than men in the cohort (57.8% vs. 42.2% respectively). Baseline data on smoking status and body mass index (BMI) were missing for 9.9% and 21.0% of patients respectively.

6.3.3 CPRD cohort - discussion

The active asthma cohort had more women than men, consistent with the established epidemiology where women have both a higher incidence and prevalence of asthma. A population based study from Finland involving 4300 people reported a higher prevalence of asthma in women compared to men (211). A UK population based study reported higher age-standardized rates of asthma for women compared to men (5.6 vs. 4.8 per 1000 person years for the year 2005) whilst another UK population based study using CPRD data demonstrated consistently higher primary care consultation rates for asthma in adult women than men (29, 212).

Approximately 87% of patients from the CPRD active asthma cohort were under the age of 60. Although excluding people coded with comorbidities may have influenced these figures, they are still in keeping with the current epidemiology showing a greater prevalence of asthma in younger than older people (212). People with comorbidities were excluded in order to avoid misclassification with other diseases where risk from beta-blockers or NSAIDs is reduced or absent which would underestimate risk in subsequent analyses. In the CPRD active asthma cohort, 45% of patients with asthma were non-smokers, 23% were ex-smokers and 22% were current smokers at baseline. This distribution of smoking status is comparable with data from the Finnish population based study in which 49% of people with asthma were non-smokers, 19% were ex-smokers and 24% were current smokers (211). These baseline characteristics are

comparable providing some validity that the CPRD asthma cohort is broadly representative of people with asthma, albeit those with active asthma, important for subsequent analyses in this thesis.

6.4 Incidence of asthma outcomes

6.4.1 Incidence of asthma outcomes - methodology

The incidence of asthma deaths, hospitalisations and primary care asthma exacerbations (PCAE) were calculated among people from the active asthma cohort linked to the ONS and HES databases for complete outcome assessment. The incidence of asthma death, asthma hospitalisation recorded in the primary position in death certificates and hospital discharges, and oral steroids for asthma was estimated for the active asthma cohort by dividing the total number of events occurring during the study period by the total person years of follow up for each type of event, with 95% confidence intervals (95% CIs) based on the Poisson distribution. For the purpose of this analysis, oral steroids for asthma were defined as any prednisolone prescription containing ≥ 5 mg strength tablets with the assumption that prescriptions issued within 14 days of the previous prescription were for the same PCAE and were counted only once.

For each type of event, the overall incidence was estimated stratified by age and gender. The incidence of asthma death was calculated per 10,000 person-years of follow up and the incidence of asthma hospitalisation and primary care asthma exacerbations was calculated per 1,000 person-years of follow up. The yearly incidence for each outcome of interest was then stratified by gender. Because the observed rates for the population may differ according to age, direct standardisation was used to control for any changes in the age structure of the active asthma cohort over the 12 year observation period. In

this regard, the European standard population was used to estimate directly age-standardised rates. Directly standardised incidence rates were obtained by first estimating the age-specific event rate for each year and gender. The event rate for each age category per year was then multiplied by the European standard population of the corresponding age category to generate the expected number of events. The expected number of events was then summed for each year and then divided by the European standard population for of all age groups to provide the standardised rate for each year. The absolute change in incidence of events during the 12 year period was determined by subtracting the incidence of events in the year 2000 from the incidence of events in the year 2011, with 95% CIs. Incidence rates were calculated in STATA v.13.

6.4.2 Incidence of asthma outcomes - results

Among the 281954 patients within the active asthma cohort, a total of 142 asthma deaths and 7511 asthma hospitalisations occurred with an overall incidence 1.5 (95% CI 1.3 to 1.8) per 10,000 person-years and 7.8 (95% CI 7.6 to 7.9) per 1,000 person-years respectively (table 12). Among the 281954 active asthma patients, a total of 287518 oral steroid prescriptions were issued. To prevent clustering, whereby multiple oral steroid prescriptions may be issued to treat the same PCAE, oral steroid prescriptions issued within 14 days of each other were assumed to be related to the same asthma exacerbation and deleted. A total of 248143 oral steroid prescriptions remained giving an overall incidence of 259.1 (95% CI 258.0 to 260.1) per 1,000 person-years. Of these 248143 prescriptions, 22874 (9.2%) consisted of either 1 mg or 2.5 mg strength prednisolone tablets rarely used for the management PCAE in adults. After exclusion of these prescriptions, the overall incidence of PCAE was 235.3 (95% CI 234.3 to 236.2) per 1,000 person-years.

Table 12. Incidence of asthma death, asthma hospitalisation, and primary care asthma exacerbation.

Characteristic	Death (95%CI)	Hospitalisation (95%CI)	PCAE (95%CI)
Gender			
Men	1.36 (1.02-1.78)	5.5 (5.3-5.7)	186.5 (185.2-187.9)
Women	1.86 (1.49-2.30)	9.4 (9.2-9.7)	271.0 (269.6-272.4)
Age			
18-29	0.32 (0.14-0.63)	11.4 (11.1-11.8)	150.1 (148.9-151.3)
30-39	0.68 (0.45-1.00)	9.0 (8.7-9.3)	190.2 (188.8-191.6)
40-49	1.41 (1.06-1.83)	7.9 (7.7-8.2)	236.5 (234.9-238.0)
50-59	1.45 (1.06-1.95)	5.4 (5.1-5.7)	271.8 (269.9-273.7)
60-69	1.85 (1.35-2.46)	5.2 (4.9-5.4)	292.5 (290.4-294.7)
>=70	4.80 (3.91-5.84)	4.8 (4.5-5.1)	354.6 (352.0-357.1)
Overall	1.50 (1.26 -1.78)	7.8 (7.6-7.9)	235.3 (234.3-236.2)

Death = per 10,000 person-years. Hospitalisation = per 1,000 person-years.

PCAE = primary care asthma exacerbation, per 1,000 person-years.

The incidence of asthma events stratified by age and gender are shown in table 12. The incidence of asthma death, asthma hospitalisation and PCAE were higher in women than men. The incidence of asthma death increased with age and was highest in patients aged 70 and over (incidence 4.8 (95% CI 3.9 to 5.8) per 10,000 person-years vs. 0.3 (95% CI 0.1 to 0.6) per 10,000 person years for patients aged between 18 and 29). In contrast, the incidence of asthma hospitalisation fell with age, being lowest in patients aged 70 and over (incidence 4.8 (95% CI 4.5 to 5.1) per 1,000 person years vs. 11.4 (95% CI 11.1 to 11.8) per 1,000 person-years for patients aged between 18 and 29). Similar to asthma deaths, the incidence of PCAE increased with age and was highest in patients aged 70 and over (incidence 354.6 (95% CI 352.0 to 357.1) per 1,000 person-years vs. 150.1 (95% CI 148.9 to 151.3) per 1,000 person years for patients aged between 18 and 29).

The directly age-standardised rates of asthma death, asthma hospitalisation and PCAE between 2000 and 2012 are shown in table 13. Over the 12 year period, the incidence of asthma death did not significantly change (incidence 1.8 (95% CI 1.1 to 2.5) per 10,000 person-years in 2000 compared to 0.8 (95% CI 0.4 to 1.3) per 10,000 person-years in 2011, figure 35). The incidence of asthma hospitalisation initially fell in 2001 and then steadily rose from a low of 6.3 (95% CI 5.7 to 6.9) per 1,000 person-years in 2001 to 9.3 (95% CI 8.6 to 10.0) per 1,000 person-years in 2011, a significant relative rise of 47.6% (95% CI 27.0 to 68.3) per 1,000 patient years. The rising incidence of asthma hospitalisation was more pronounced in women than men, with a significant relative rise of 54.0% (95% CI 36.8 to 72.4) per 1,000 patient years for women vs. a significant relative rise of 31.9% (95% CI 10.6 to 55.3) per 1,000 person-years in men (figure 36).

The incidence of PCAE initially fell in 2001 and then rose from a low of 195.3 (95% CI 192.2 to 198.5) per 1,000 person-years in 2001 to 249.4 (95% CI 245.9-253.0) per 1,000 person-years in 2011, a significant relative rise of 27.7% (95% CI 24.3 to 31.1) per 1,000 person-years (table 13). Again, the rising incidence of PCAE was more pronounced in women than men, with a significant relative rise of 32.3% (95% CI 29.0 to 35.6) per 1,000 person-years in women vs. a significant relative rise of 20.2% (95% CI 16.5 to 23.8) per 1,000 person-years in men, between 2001 and 2011 (figure 37).

Table 13. Directly age-standardised incidence of asthma death, asthma hospitalisation and primary care asthma exacerbations.

Year	Incidence in women (95%CI)			Incidence in men (95%CI)		
	Death	Hospitalisation	PCAE	Death	Hospitalisation	PCAE
2000	1.01 (0.40-2.00)	9.9 (9.2-10.6)	231.7 (228.3-235.2)	2.50 (1.50-3.90)	5.7 (5.2-6.3)	183.8 (180.8-186.9)
2001	1.19 (0.50-2.20)	7.6 (7.0-8.2)	217.4 (214.1-220.7)	0.88 (0.30-1.80)	4.7 (4.2-5.2)	166.3 (163.4-169.2)
2002	1.78 (0.90-3.00)	7.9 (7.3-8.6)	231.8 (228.4-235.3)	2.43 (1.40-3.80)	4.4 (4.0-4.9)	177.6 (174.6-180.6)
2003	1.33 (0.60-2.40)	9.4 (8.7-10.1)	236.7 (233.3-240.1)	1.27 (0.60-2.30)	5.4 (4.9-6.0)	167.6 (164.7-170.5)
2004	1.94 (1.00-3.10)	9.4 (8.7-10.1)	236.8 (233.4-240.3)	0.60 (0.20-1.40)	6.1 (5.5-6.6)	174.9 (171.9-177.9)
2005	0.65 (0.20-1.40)	10.0 (9.3-10.7)	250.7 (247.1-254.2)	1.74 (0.90-2.90)	6.2 (5.7-6.8)	176.3 (173.4-179.3)
2006	1.58 (0.80-2.70)	9.6 (8.9-10.3)	252.0 (248.4-255.5)	1.10 (0.50-2.10)	5.3 (4.8-5.8)	176.4 (173.4-179.3)
2007	1.09 (0.50-2.10)	10.8 (10.0-11.5)	274.6 (271.0-278.3)	1.65 (0.80-2.80)	6.0 (5.4-6.5)	196.1 (193.0-199.2)
2008	0.91 (0.40-1.80)	12.2 (11.4-13.0)	290.5 (286.7-294.3)	0.54 (0.10-1.30)	5.9 (5.3-6.4)	203.8 (200.6-207.0)
2009	0.72 (0.20-1.60)	11.5 (10.8-12.3)	282.5 (278.8-286.3)	1.10 (0.50-2.10)	5.6 (5.1-6.1)	196.5 (193.4-199.6)
2010	2.32 (1.40-3.60)	10.7 (10.0-11.4)	287.6 (283.8-291.4)	1.49 (0.70-2.60)	5.1 (4.7-5.7)	203.9 (200.8-207.1)
2011	0.84 (0.30-1.80)	11.7 (11.0-12.5)	287.2 (283.4-291.0)	0.74 (0.20-1.60)	6.2 (5.7-6.8)	199.9 (196.7-203.0)

Death = per 10,000 person-years. Hospitalisation = per 1,000 person-years.

PCAE = primary care asthma exacerbation, per 1,000 person-years.

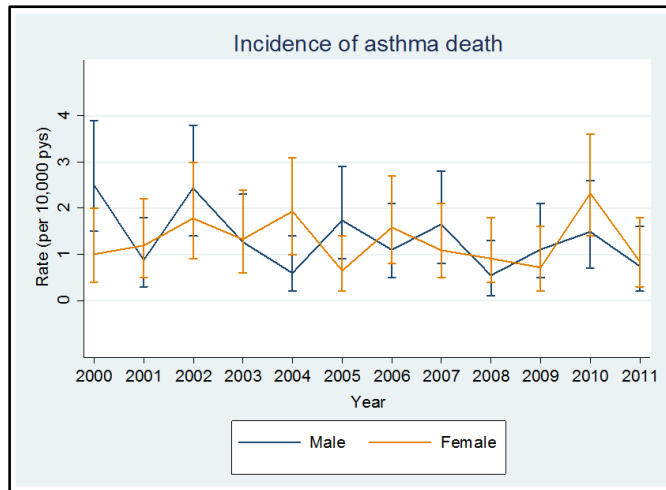


Figure 35. Direct age-standardised incidence of asthma death 2000 to 2012.

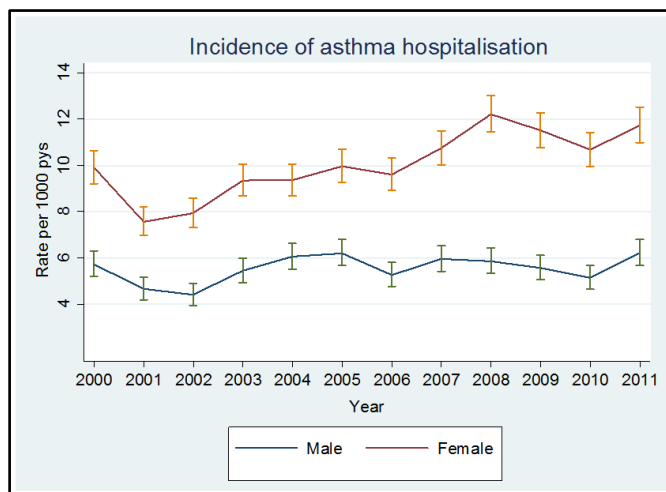


Figure 36. Direct age-standardised incidence of asthma hospitalisation 2000 to 2012.

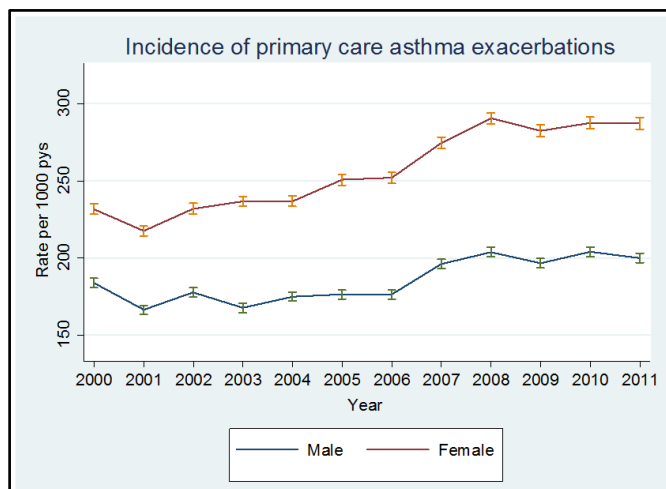


Figure 37. Direct age-standardised incidence of PCAE 2000 to 2012.

6.4.3 Incidence of asthma outcomes - discussion

The incidence of asthma death in the CPRD active asthma cohort was 1.5 per 10,000 person-years, increased with age and remained fairly level over the study period.

National statistics such as those available from the Scottish Public Health Observatory in Scotland and the Office for National Statistics in England report death statistics for asthma. In England in 2013, 344 adult asthma deaths occurred in men and 742 in women however no death rate was provided to directly compare (213). In Scotland in 2012, 20 asthma deaths occurred in men and 69 in women with an overall asthma death rate of 1 per 100,000 in men and 3 per 100,000 total population in women (45).

However, the denominator used for the 2012 Scottish death rate was the general population as opposed to an asthma population so direct comparison is again not possible. Despite these limitations national statistics from both England and Scotland show strong associations between increasing age and increasing numbers of asthma deaths. A large UK study describing trends in asthma events from 1955 to 2004 also demonstrated increasing asthma death rate with age. In that study asthma death rate among people aged 15 to 44 was approximately 0.6 per 100,000 person years compared to approximately 12 per 100,000 person years in people aged 65 years and over. Similarly, the recently published National Review of Asthma Deaths in the UK also demonstrated that asthma death was more common among older adults (56).

The overall incidence of asthma hospitalisation in the CPRD active asthma cohort was 7.8 per 1,000 person-years. The incidence of asthma hospitalisation was higher in women than men, increased over the study period (particularly in women) and fell significantly with increasing age. From 2011 to 2012, 40243 asthma hospitalisations occurred in the UK in people aged 15 years and over (56). In Scotland from 2012 to

2013, the incidence of asthma hospitalisation in men and women was 51.1 and 70.2 per 100,000 population respectively and consistently higher for women as seen with the CPRD active asthma cohort (40). However, Scottish rates defined incidence as first hospital admission for asthma without a previous hospital admission for asthma and therefore do not account for multiple admissions for the same individual making direct comparisons difficult. Other Scottish national statistics have reported an incidence of asthma hospitalisation for 2011 to 2012 of 152 per 100,000 population (which includes all ages and genders) (214). Meanwhile, a study investigating the effectiveness of ICS at preventing asthma hospitalisation in Canada reported a higher incidence of asthma hospitalisation of 42.4 per 1,000 asthma patients per year although this was for a population aged 5 to 44 years in which the incidence of asthma hospitalisation is also known to be greater (215).

The rate of asthma hospitalisation in the CPRD active asthma cohort increased between 2001 and 2011 by around 54% for women and 32% for men. In comparison, the incidence of asthma hospitalisation (defined as first ever admission with asthma) rose by 122% in Scotland between 1981 and 1997, again with greater increases in women than men (143% vs. 101%) (37). Data from HES in England also confirms the increased asthma hospitalisation rate in women compared to men and among younger people with asthma compared to older people.

The overall incidence of PCAE in the CPRD active asthma cohort was 235.3 per 1,000 person years. The incidence of PCAE was higher in women than men, increased significantly with increasing age and increased over the study period. Over this period, national statistics for the urgent management of asthma in primary care have not been

produced so no figures are available for comparison. It is possible that the incidence of PCAE measured in this chapter is an overestimate because steroids have a wide range of uses in primary care (although the selection criteria were intended to minimise this), but whether or by how much any overestimation has occurred is uncertain.

In many instances direct comparisons with national statistics were not possible because different denominators were used, although changing patterns according to age and gender are reassuringly similar. It should therefore be highlighted that the incidence of asthma hospitalisation and PCAE appear to be increasing particularly in women, and future research to further examine the reasons for these increases is required.

6.5 Risk factor assessment

6.5.1 Risk factor assessment - methodology

A nested case-control study was used to determine risk factors for each asthma event as previously defined (chapter 2, page 70), in order to inform the subsequent modelling. For asthma deaths and hospitalisations, up to 10 controls were randomly selected and matched to each case on calendar year of cohort entry and whether patients were diagnosed with asthma before the age of 45 using incidence density sampling. For PCAEs, up to 4 controls were randomly selected in the same manner, the smaller number reflecting that there were many more individuals with PCAE reducing the potential pool of controls. The date of the risk set was the index date for the cases and subjects were eligible to be used as controls in multiple sampled risk sets. For all cases and controls, information was obtained on age, gender, social deprivation (as measured by the index of multiple deprivation), BMI, smoking status, Charlson comorbidity score, asthma medication, primary care asthma reviews, history of nasal polyps, chronic

rhinosinusitis, urticaria, allergy, anxiety, respiratory tract infections and previous asthma hospitalisation. Exposure to asthma medication was based upon prescriptions issued within 90 days of the index date.

Multiple imputation with fully conditional specification was used to impute missing data on height, weight and smoking status. The nested case control study was analysed as per the general methods chapter (chapter 2, page 70). In summary, Chi-squared test and analysis of variance was used to determine significant differences between categorical and continuous patient characteristics respectively. Multivariate conditional logistic regression using a fully saturated model was used to compute adjusted incidence rate ratios (IRR) for selected risk factors assessed using a 90 day risk window.

6.5.2 Risk factor assessment - results

Asthma deaths

Table 14 describes the characteristics of 142 cases of asthma death and their 1420 controls. Cases died of asthma at a mean age of 60 years and were more likely to be women (62%). Cases were significantly older than controls and had significantly higher use of LABAs, leukotriene antagonists, methylxanthines, oral steroids and SABAs in the 90 days prior to the index date. There were significantly more current smokers and significantly fewer ex-smokers and non-smokers among cases than controls. Cases were significantly more likely to have: been hospitalised for asthma in the past; had a RTI in the 90 days before index date; a lower BMI; and a higher Charlson co-morbidity score.

Table 14. Characteristics of patients for the analysis of asthma deaths in the risk factor analysis.

Characteristics	Cases N=142	Controls N=1420	p-value
Age (years)	60.0 (17.3)	54.0 (16.5)	0.000*
Female gender	88 (62.0)	871 (61.3)	0.882
Asthma medication in the last 90 days			
▪ ICS	61 (43.0)	628 (44.2)	0.772
▪ LABA	27 (19.0)	142 (10.0)	0.001
▪ LABAICS	33 (23.2)	289 (20.4)	0.447
▪ Leukotriene antagonist	8 (5.6)	44 (3.1)	0.108
▪ Methylxanthine	15 (10.6)	31 (2.2)	0.000
▪ Mean no. of SABA prescriptions	2.5 (2.5)	1.1 (1.3)	0.000*
▪ Oral steroid	49 (34.5)	105 (7.4)	0.000
Comorbidity			
▪ Nasal polyps	10 (7.0)	68 (4.8)	0.240
▪ Urticaria	6 (4.2)	79 (5.6)	0.543
▪ Allergy	41 (28.9)	391 (27.5)	0.734
▪ Anxiety [‡]	5 (3.5)	30 (2.1)	0.280
▪ Mean BMI (SD)	26.1 (5.3)	28.0 (6.1)	0.001*
▪ Mean Charlson co-morbidity score	1.8 (1.3)	1.5 (1.1)	0.002*
Smoking status			
▪ Current smoker	32 (22.5)	212 (14.9)	0.017
▪ Ex-smoker	39 (27.5)	523 (36.8)	0.027
▪ Non-smoker	40 (28.2)	619 (43.6)	0.000
▪ Missing	31 (21.8)	66 (4.6)	0.000
Previous hospitalisation for asthma	44 (31.0)	56 (3.9)	0.000
RTI	23 (16.2)	95 (6.7)	0.000
Asthma review [‡]	56 (39.4)	565 (39.8)	0.935

*Continuous variable analysed using ANOVA, otherwise variables are categorical analysed using the Chi-square test. SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection, BMI = Body mass index. [‡] Within 365 days of the index date. Cases and controls matched on calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

Asthma hospitalisations

Table 15 describes the characteristics of 5016 cases of asthma hospitalisation and their 50140 controls. Cases were hospitalised for asthma at a mean age of 41.4 years and were more likely to be female (68%). Cases were significantly younger than controls but differences were small in absolute terms (41.4 vs. 42.6 years respectively). Cases had significantly higher use of all types of asthma therapy in the 90 days prior to the index date. Cases were significantly more likely to have a history of nasal polyps, urticaria, allergy and anxiety. There were significantly more current smokers and non-smokers among cases than controls. Cases were significantly more likely to have: been hospitalised for asthma in the past; had a RTI in the 90 days before index date; had an asthma review in the preceding year; and have a higher BMI.

Table 15. Characteristics of patients for the analysis of asthma hospitalisations in the risk factor analysis.

Characteristics	Cases N=5016	Controls N=50140	p-value
Age (years)	41.4 (16.9)	42.6 (16.5)	0.000*
Female gender	3416 (68.1)	28512 (56.9)	0.000
Asthma medication in the last 90 days			
▪ ICS	2168 (43.2)	19164 (38.2)	0.000
▪ LABA	882 (17.6)	3211 (6.4)	0.000
▪ LABAICS	1326 (26.4)	8036 (16.0)	0.000
▪ Leukotriene antagonist	406 (8.1)	1088 (2.2)	0.000
▪ Methylxanthine	251 (5.0)	554 (1.1)	0.000
▪ Mean no. of SABA prescriptions	2.0 (1.9)	1.0 (1.2)	0.000*
▪ Oral steroid	1824 (36.4)	2612 (5.2)	0.000
Comorbidity			
▪ Nasal polyps	209 (4.2)	1488 (3.0)	0.000
▪ Urticaria	344 (6.9)	2940 (5.9)	0.005
▪ Allergy	1377 (27.5)	11633 (23.2)	0.000
▪ Anxiety [‡]	152 (3.0)	1173 (2.3)	0.002
▪ Mean BMI (SD)	28.2 (7.0)	27.2 (6.1)	0.000*
▪ Mean Charlson co-morbidity score	1.3 (0.9)	1.3 (0.8)	0.000*
Smoking status			
▪ Current smoker	1338 (26.7)	10259 (20.5)	0.000
▪ Ex-smoker	1448 (28.9)	14805 (29.5)	0.329
▪ Non-smoker	1946 (38.8)	21972 (43.8)	0.000
▪ Missing	284 (5.7)	3104 (6.2)	0.137
Previous hospitalisation for asthma	1016 (20.3)	1305 (2.6)	0.000
RTI	800 (15.9)	2949 (5.9)	0.000
Asthma review [‡]	2046 (40.8)	18833 (37.6)	0.000

*Continuous variable analysed using ANOVA, otherwise variables are categorical analysed using the Chi-square test. SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection, BMI = Body mass index. [‡] Within 365 days of the index date. Cases and controls matched on calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

Primary Care Asthma Exacerbations

Table 16 describes the characteristics of 31771 cases of PCAE and their 127080 controls. Cases experienced their PCAE at a mean age of 42.9 years and were more likely to be female (63%). Cases were significantly older than controls but differences were small in absolute terms (42.9 vs. 42.2 years respectively). Cases had significantly higher use of all types of asthma therapy in the 90 days prior to the index date. Cases were significantly more likely to have a history of nasal polyps, urticaria, allergy and anxiety. There were significantly more current smokers and ex-smokers and fewer non-smokers among cases than controls. Cases were significantly more likely to: have been hospitalised for asthma in the past; have had a RTI in the 90 days before index date; have had an asthma review in the preceding year; have a higher BMI; and have a lower Charlson co-morbidity score.

Table 16. Characteristics of patients for the analysis of primary care asthma exacerbations in the risk factor analysis.

Characteristics	Cases N=31771	Controls N=127080	p-value
Age (years)	42.9 (16.7)	42.2 (17.2)	0.000*
Female gender	19951 (62.8)	69906 (55.0)	0.000
Asthma medication*			
▪ ICS	14225 (44.8)	48407 (38.1)	0.000
▪ LABA	2022 (6.4)	5152 (4.1)	0.000
▪ LABAICS	4783 (15.1)	14163 (11.1)	0.000
▪ Leukotriene antagonist	601 (1.9)	1369 (1.1)	0.000
▪ Methylxanthine	283 (0.9)	697 (0.5)	0.000
▪ Mean no. of SABA prescriptions	1.2 (1.2)	0.9 (1.0)	0.000*
▪ Oral steroid	-	-	
Comorbidity			
▪ Nasal polyps	933 (2.9)	2705 (2.1)	0.000
▪ Urticaria	2029 (6.4)	6144 (4.8)	0.000
▪ Allergy	7729 (24.3)	25652 (20.2)	0.000
▪ Anxiety [‡]	873 (2.7)	2764 (2.2)	0.000
▪ Mean BMI (SD)	27.8 (7.7)	27.0 (6.4)	0.000*
▪ Mean Charlson co-morbidity score	1.2 (0.8)	1.3 (0.8)	0.000*
Smoking status			
▪ Current smoker	7514 (23.7)	25218 (19.8)	0.000
▪ Ex-smoker	9172 (28.9)	35830 (28.2)	0.017
▪ Non-smoker	13111 (41.3)	56533 (44.5)	0.000
▪ Missing	1974 (6.2)	9499 (7.5)	0.000
Previous hospitalisation for asthma	1500 (4.7)	2551 (2.0)	0.000
RTI*	4160 (13.1)	6644 (5.2)	0.000
Asthma review [‡]	11845 (37.3)	42543 (33.5)	0.000

*Continuous variable analysed using ANOVA, otherwise variables are categorical analysed using the

Chi-square test. SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-

agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting

beta2-agonist, RTI = respiratory tract infection, BMI = Body mass index. [‡] Within 365 days of the index

date. Cases and controls matched on calendar year of cohort entry and whether patients were diagnosed

with asthma under the age of 45 years only.

Multivariate risk factor analysis using conditional logistic regression

Table 17 summarizes the adjusted incidence rate ratios (IRR) for different risk factors and asthma outcomes. The following risk factors were significantly associated with an increase in the relative incidence of asthma death: age (greatest in patients aged 70 and older IRR 37.14 (95% CI 7.93 to 174.1) compared to people aged 18 to 29); SABA prescription (IRR 1.52 (95% CI 1.33 to 1.74) for each additional prescription); treatment with an oral steroid (IRR 3.40 (95% CI 1.85 to 6.25)); and previous hospitalisation for asthma (IRR 9.04 (95% CI 4.80 to 17.00)).

The following risk factors were significantly associated with a decrease in the relative incidence of asthma death: treatment with an ICS (IRR 0.41 (95% CI 0.24 to 0.70); treatment with a LABA/ICS (IRR 0.48 (95% CI 0.25 to 0.94)); increasing BMI (IRR 0.92 (95% CI 0.89 to 0.96)) and being a non-smoker (IRR 0.52 (95% CI 0.29 to 0.94)). The relative incidence of asthma death was higher in patients with increasing Charlson co-morbidity score and increasing social deprivation but this association was not statistically significant (IRR 1.11 (95% CI 0.94 to 1.31) and IRR 1.06 (95% CI 0.98 to 1.15) per decile of the index of multiple deprivation respectively). There were no significant differences with any other risk factor assessed.

Table 17. Association between asthma outcomes and risk factor assessment in the risk factor analysis.

Characteristic	Death		Hospitalisation		PCAE	
	IRR	95%CI	IRR	95%CI	IRR	95%CI
Age category						
▪ 18-29	Ref	Ref	Ref	Ref	Ref	Ref
▪ 30-39	3.28	0.86-12.55	0.78	0.71-0.86	1.10	1.06-1.15
▪ 40-49	7.00	1.93-25.43	0.60	0.54-0.67	1.16	1.11-1.22
▪ 50-59	12.41	3.09-49.83	0.49	0.42-0.57	1.20	1.13-1.28
▪ 60-69	13.41	3.01-59.84	0.51	0.43-0.62	1.31	1.22-1.41
▪ ≥70	37.14	7.93-174.1	0.47	0.38-0.58	1.31	1.21-1.43
Female gender	0.87	0.54-1.39	1.44	1.34-1.55	1.37	1.33-1.41
Increasing deprivation [€]	1.06	0.98-1.15	1.02	1.01-1.03	1.03	1.02-1.03
Asthma therapy*						
▪ ICS	0.41	0.24-0.70	0.84	0.78-0.92	1.13	1.09-1.16
▪ LABA	1.35	0.70-2.62	2.13	1.91-2.37	1.48	1.40-1.57
▪ LABAICS	0.48	0.25-0.94	1.22	1.11-1.34	1.37	1.31-1.43
▪ Leukotriene antagonist	0.84	0.27-2.61	1.23	1.05-1.44	1.39	1.24-1.55
▪ Methylxanthine	2.08	0.83-5.25	1.39	1.13-1.72	1.16	1.00-1.36
▪ No. of SABAs [¥]	1.52	1.33-1.74	1.38	1.34-1.41	1.24	1.23-1.26
▪ Oral steroid	3.40	1.85-6.25	6.35	5.83-6.93	n/a	n/a
Comorbidity						
▪ Nasal polyps	1.23	0.49-3.06	1.31	1.10-1.57	1.49	1.37-1.62
▪ Urticaria	0.80	0.28-2.29	1.00	0.87-1.15	1.28	1.21-1.36
▪ Allergy	0.86	0.52-1.41	0.99	0.91-1.07	1.20	1.16-1.24
▪ Anxiety	1.82	0.54-6.07	1.07	0.88-1.31	1.12	1.02-1.22
▪ BMI [¥]	0.92	0.89-0.96	1.01	1.01-1.02	1.01	1.01-1.01
▪ Charlson score [¥]	1.11	0.94-1.31	1.07	1.03-1.10	0.92	0.90-0.93
Smoking status						
▪ Current smoker	Ref	Ref	Ref	Ref	Ref	Ref
▪ Ex-smoker	0.54	0.28-1.04	0.86	0.78-0.94	0.96	0.92-0.99
▪ Non-smoker	0.52	0.29-0.94	0.81	0.74-0.88	0.90	0.87-0.93
Prior asthma hospitalisation	9.04	4.80-17.00	6.27	5.62-7.00	2.18	2.02-2.35
RTI*	1.95	0.97-3.92	1.63	1.46-1.81	2.44	2.32-2.56
Asthma review ^δ	0.92	0.53-1.60	0.96	0.88-1.04	1.39	1.34-1.44

PCAE= Primary care asthma exacerbation. Ref = reference category. *= In the 90 days prior to index

date. €= Per increasing unit change in IMD decile. δ = In the 365 days prior to index date. ¥ = Mean

value. Cases and controls matched on calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

The following risk factors were significantly associated with an increase in the relative incidence of asthma hospitalisation (table 17): SABA prescription (IRR 1.38 (95% CI 1.34 to 1.41) for each additional prescription); treatment with an oral steroid (IRR 6.35 (95% CI 5.83 to 6.93); treatment with a LABA or LABAICS (IRR 2.13 (95% CI 1.91 to 2.37) and IRR 1.22 (95% CI 1.11 to 1.34) respectively); treatment with a leukotriene antagonist or methylxanthine (IRR 1.23 (95% CI 1.05 to 1.44) and IRR 1.39 (95% CI 1.13 to 1.72) respectively); previous hospitalisation for asthma (IRR 6.27 (95% CI 5.62 to 7.00)); developing a RTI (IRR 1.63 (95% CI 1.46 to 1.81)); female gender (IRR 1.44 (95% CI 1.34 to 1.55)); a history of nasal polyposis (IRR 1.31 (95% CI 1.10 to 1.57)); increasing BMI (IRR 1.01 (95% CI 1.01 to 1.02)); increasing Charlson co-morbidity score (IRR 1.07 (95% CI 1.03 to 1.10)) and increasing social deprivation (IRR 1.02 (95% CI 1.01 to 1.03) per decile of the index of multiple deprivation). The following risk factors were significantly associated with a decrease in the relative incidence of asthma hospitalisation: increasing age, being smallest in patients aged 70 years and older (IRR 0.47 (95% CI 0.38 to 0.58)); treatment with an ICS (IRR 0.84 (95% CI 0.78 to 0.92)); being an ex-smoker (IRR 0.86 (95% CI 0.78 to 0.94)) or a non-smoker (IRR 0.81 (95% CI 0.74 to 0.88)).

The following risk factors were significantly associated with an increase in the relative incidence of PCAE (table 17): SABA prescription (IRR 1.24 (95% CI 1.23 to 1.26) for each additional prescription); treatment with an ICS (IRR 1.13 (95% CI 1.09 to 1.16)); treatment with a LABA or LABAICS (IRR 1.48 (95% CI 1.40 to 1.57) and IRR 1.37 (95% CI 1.31 to 1.43) respectively); treatment with a leukotriene antagonist or methylxanthine (IRR 1.39 (95% CI 1.24 to 1.55) and IRR 1.16 (95% CI 1.00 to 1.36) respectively); previous hospitalisation for asthma (IRR 2.18 (95% CI 2.02 to 2.35));

developing a RTI (IRR 2.44 (95% CI 2.32 to 2.56)); female gender (IRR 1.37 (95% CI 1.33 to 1.41)); increasing age being greatest in people over 60 years of age (IRR 1.31 (95% CI 1.21 to 1.43)); a history of nasal polyposis (IRR 1.49 (95% CI 1.37 to 1.62)); a history of urticaria and allergy (IRR 1.28 (95% CI 1.21 to 1.36) and IRR 1.20 (95% CI 1.16 to 1.24) respectively); a recent history of anxiety (IRR 1.12 (95% CI 1.02 to 1.22)); increasing BMI (IRR 1.01 (95% CI 1.01 to 1.01)); and attending an asthma review in the previous year (IRR 1.39 (95% CI 1.34 to 1.44)); and increasing social deprivation (IRR 1.03 (95% CI 1.02 to 1.03) per decile of the index of multiple deprivation). The following risk factors were significantly associated with a decrease in the relative incidence of PCAE: being an ex-smoker (IRR 0.96 (95% CI 0.92 to 0.99)) or a non-smoker (IRR 0.90 (95% CI 0.87 to 0.93)); and increasing Charlson co-morbidity score (IRR 0.92 (95% CI 0.90 to 0.93)).

6.5.3 Risk factor assessment - discussion

In the CPRD active asthma cohort, the relative incidence of asthma death and PCAE increased with age. This association has also been found in a retrospective cohort study where 30 day case-fatality following hospitalisation for asthma in adults in Scotland increased with age (42). In primary care, increasing age has also been associated with poor asthma control in general practice (48). This association is consistent with incidence rates reported in this thesis and with national statistics as previously discussed in this chapter.

The falling incidence of asthma hospitalisation with increasing age has not previously been described. National statistics do not report asthma hospitalisation rates by age group making it difficult to know whether this result is biased. Evidence from the

National Enquiry of Asthma Deaths suggests that accuracy of coding may be more unreliable for older adults (56). In that enquiry, the expert panel agreed that clinical findings matched the coding of asthma as the underlying cause of death in only around 50% of people aged 75 years and older. However, agreement could not be reached in several of these cases due to insufficient information rather than coding error. This finding may also be an artefact of excluding people with comorbid respiratory conditions or due to differences in asthma discharge recording in older adults. Incidence of asthma hospitalisation depended upon asthma recorded in the primary position and it may be that older adults may have other comorbidities recorded in the primary position upon discharge than younger adults. However, including cases where asthma is recorded in other positions would affect the sensitivity of this measure when investigating risk associated with beta-blockers and NSAIDs in subsequent chapters.

Unlike asthma hospitalisation and PCAE, gender was not a significant risk factor for asthma death in the adjusted analysis as previously reported in a study of 30 day case-fatality following asthma hospitalisation in adults (42). ICS therapy in this study was significantly associated with a reduced rate of asthma death and hospitalisation by 57% and 27% respectively. A previous nested case control study investigating the effectiveness of ICS reported a 21% reduced rate of asthma death with each additional canister of ICS used in the previous year with the rate of asthma death increasing in the three months following discontinuation compared to those people who continued ICS therapy (59). In a separate nested case control study involving asthma patients aged 5 to 44 years, regular use of ICS was associated with a 31% reduction in the rate of asthma hospitalisation and a 39% reduction in the rate of asthma hospital readmission (215). However, current use of ICS was associated with an increased risk of PCAE in the

CPRD active asthma cohort. This is more likely to reflect the persons underlying severity of asthma (i.e. people at step 2 may have more severe asthma than those at step 1) or that people were commenced on ICS shortly before an asthma exacerbation which was not prevented by ICS therapy alone. The increasing use of SABAs, oral steroids and previous hospitalisation for asthma were consistently associated with an increased risk of adverse asthma events as previously established. Indeed, frequent need for reliever therapy such as using more than 2 canisters of SABA per month is a marker of poor asthma control and a risk factor for fatal attacks (57). The association with remaining asthma medications is again likely to reflect the persons underlying severity of asthma rather than to be causal although large clinical trials attempting to clarify the safety of LABAs in asthma have been mandated by the FDA and are currently underway.

Within the CPRD active asthma cohort, ex-smokers and non-smokers had a reduced rate of asthma events compared to smokers. This is in keeping with the current understanding that smoking is associated with poor asthma control and adverse respiratory events (48). People with a history of nasal polyps had an increased rate of asthma hospitalisation and PCAE which probably represents the increased asthma morbidity which occurs in people with the AERD phenotype (201). Increasing BMI was associated with an increased rate of asthma hospitalisation and PCAE but a reduced rate of asthma death which cannot be fully explained. Leptin and adiponectin levels may influence airway hyper-responsiveness including pro-inflammatory and anti-inflammatory cytokines and a recent study found that increasing BMI was independently associated with AERD (201). Increasing comorbidity was associated with increased rate of asthma death and hospitalisation which has been reported

elsewhere however the reduced rate of PCAE with increasing comorbidity again cannot be fully explained (42). Other risk factors were significantly associated with PCAE such as allergy and attendance at primary care asthma reviews but had no significant relationship on asthma deaths and hospitalisations.

Overall, the risk factor assessment conducted with the CPRD active asthma cohort identified similar risk factors which have been reported elsewhere such as SABA use, the effect of ICS therapy and smoking status. This provides some reassurance to the quality of the data and its representativeness of people with active asthma, and identifies important confounders to adjust for in the main analyses. Some findings remain difficult to explain such as the falling incidence of asthma hospitalisation with age, the relationship between BMI and asthma deaths, and the relationship between comorbidity and PCAE which would benefit from further investigation. However, some other potential risk factors have not been evaluated because the data is not available in GP clinical records, including environmental risk factors such as air pollution and area of residence

6.6 Drug utilisation studies

6.6.1 Drug utilisation studies - methodology

For patients in the active asthma cohort, the prevalence of oral beta-blocker and NSAID prescribing was calculated on a quarterly basis between 1 January 2000 and 31 December 2011. The numerator consisted of the number of patients issued one or more beta-blocker or NSAID prescriptions in any particular quarter and the denominator consisted of the total number of patients with active asthma present in the cohort during the same quarter. The prevalence of beta-blocker or NSAID prescribing was determined by dividing the numerator by the denominator (as previously defined) and multiplied by 100. The relative change in the prevalence of beta-blocker and NSAID prescribing over the study period was determined by subtracting the prevalence during the first quarter of 2000 from the prevalence during the last quarter of 2011, with 95% confidence intervals (95% CIs). Oral beta-blockers were grouped into selective and non-selective agents whilst NSAIDs were grouped into one of four categories: COX-2 inhibitors; other NSAIDs with 5-50 fold COX-2 selectivity; other NSAIDs with <5 fold COX-2 selectivity; and non-selective NSAIDs. Please refer to chapter 2 (page 69) for further details.

6.6.2 Drug utilisation studies - results

Oral beta-blockers

A total of 10266 patients from the active asthma cohort (3.6%, 95% CI 3.6 to 3.7) were prescribed 154664 oral beta-blocker prescriptions during cohort follow-up. Of the 10266 patients prescribed an oral beta-blocker, 4006 patients (39.0%, 95% CI 38.1 to 40.0) received an average of 8.9 prescriptions (95% CI 8.3 to 9.4) for non-selective beta-blockers compared to 6633 patients (64.6%, 95% CI 63.7 to 65.5) who received an

average of 18.0 prescriptions (95% CI 17.4 to 18.6) for selective beta-blockers.

Selective beta-blockers accounted for 77.1% of all oral beta-blocker prescriptions issued. Oral beta-blocker prescribing to patients with active asthma varied significantly by age and gender (table 18). Selective beta-blocker prescribing steadily increased with age (Chi-square test $p < 0.001$) being greatest in patients aged 70 and over compared to non-selective beta-blockers which were more commonly prescribed to younger patients. Women were prescribed significantly more beta-blockers (both selective and non-selective) than men (72.5% of patients prescribed non-selective and 58.1% of patients prescribed oral selective beta-blockers were women, Chi-square test $p < 0.001$).

Of the 4006 patients prescribed non-selective beta-blockers, the most commonly prescribed drugs were propranolol (67.0%) and sotalol (16.1%) with a mean daily dose of 69.8 mg (95% CI 66.3 to 67.8) and 111.6 mg (95% CI 109.7 to 113.5) respectively (table 19). 2290 patients (57.2%) were issued more than one oral non-selective beta-blocker prescription.

Of the 6633 patients prescribed selective beta-blockers, the most commonly prescribed drugs were atenolol (50.3%) and bisoprolol (37.8%) with a mean daily dose of 46.6 mg for atenolol (95% CI 46.4 to 46.8) and 4.1 mg for bisoprolol (95% CI 4.1 to 4.1). 5581 patients (84.1%) were issued more than one oral selective beta-blocker prescription.

Table 18. Distribution of oral beta-blocker exposure at any point during cohort follow-up by age, gender and selectivity in patients with active asthma.

Variable	Selective No. (%)	Non-selective No. (%)	Any beta- blocker No. (%)
Age group			
▪ 18-29	174 (18.0)	808 (82.0)	969 (100.0)
▪ 30-39	385 (29.9)	936 (70.1)	1287 (100.0)
▪ 40-49	928 (53.0)	868 (47.0)	1750 (100.0)
▪ 50-59	1598 (72.0)	693 (28.0)	2219 (100.0)
▪ 60-69	2015 (81.3)	552 (18.7)	2477 (100.0)
▪ ≥70	2355 (86.7)	465 (13.3)	2716 (100.0)
Gender			
▪ Male	2776 (74.0)	1101 (26.0)	3748 (100.0)
▪ Female	3857 (59.2)	2905 (40.8)	6518 (100.0)

Percentages are row percentages

Table 19. Characteristics of oral beta-blocker exposure at any point during cohort follow-up in patients with active asthma.

Beta-blocker		No. prescriptions (%)	Mean daily dose (SD)
Non-selective	Carvedilol	3740 (10.6)	20.8 (26.7)
	Labetalol	870 (2.5)	332.7 (305.2)
	Nadolol	178 (0.5)	40.2 (29.0)
	Oxprenolol	948 (2.7)	108.0 (74.4)
	Pindolol	56 (0.2)	7.5 (4.9)
	Propranolol	23751 (67.0)	69.8 (58.6)
	Sotalol	5713 (16.1)	111.6 (72.3)
	Timolol	192 (0.5)	14.7 (8.7)
	Total	35448 (100.0)	-
Selective	Acebutolol	129 (0.11)	431.0 (425.7)
	Atenolol	59935 (50.3)	46.6 (25.1)
	Bisoprolol	45036 (37.8)	4.1 (3.2)
	Celiprolol	2330 (2.0)	244.7 (111.4)
	Metoprolol	7432 (6.2)	93.3 (272.8)
	Nebivolol	4354 (3.7)	4.3 (1.9)
	Total	119216 (100.0)	-

The quarterly prevalence of oral beta-blocker prescribing is shown in figure 38.

Between the first quarter of 2000 and the last quarter of 2011, the quarterly prevalence of any oral beta-blocker prescribing (both non-selective and selective) rose from a low of 1.2% (95% CI 1.1 to 1.2) in the first quarter of 2000 to a high of 3.4% (95% CI 3.3 to 3.5) in the last quarter of 2011, a significant relative rise of 196.5% (95% CI 183.5 to 208.7) over the 12 year period. The quarterly prevalence of oral selective beta-blocker prescribing rose from a low of 0.85% (95% CI 0.80 to 0.90) in the first quarter of 2000 to a high of 2.84% (95% CI 2.76 to 2.9) in the last quarter of 2011, a significant relative rise of 234.1% (95% CI 218.8 to 249.4) over the 12 year period. The quarterly prevalence of oral non-selective beta-blocker prescribing rose from a low of 0.31% (95% CI 0.28 to 0.34) in the first quarter of 2000 to a high of 0.58% (95% CI 0.54 to 0.61) in the last quarter of 2011, a significant relative rise of 87.1% (95% CI 64.5 to 106.5) over the 12 year period.

For individual beta-blocker drugs, the quarterly prevalence of atenolol prescribing rose from 0.57% (95% CI 0.53 to 0.61) in the first quarter of 2000 to a high of 0.91% (95% CI 0.87 to 0.96) in the fourth quarter of 2004 before starting to fall again to 0.65% (95% CI 0.61 to 0.68) by the last quarter of 2011 (figure 38b). In contrast, the quarterly prevalence of bisoprolol prescribing rose over the entire 12 year period from 0.16% (95% CI 0.14 to 0.19) in the first quarter of 2000 to a high of 1.91% (95% CI 1.85 to 1.97) in the last quarter of 2011, a significant relative rise of 1093% (95% CI 1038 to 1144).

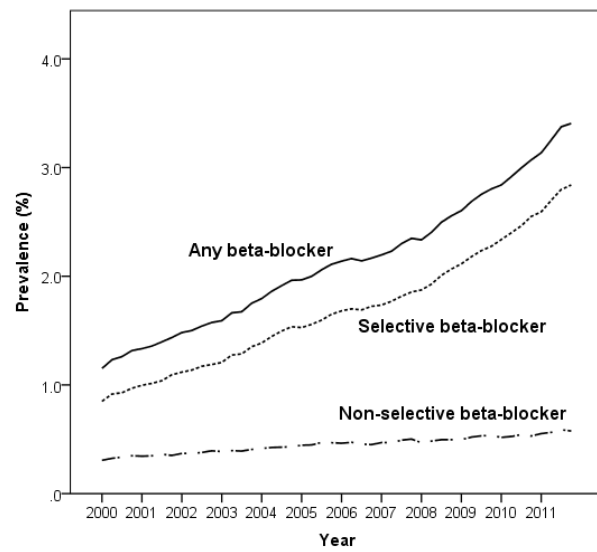


Figure 38a. Oral beta-blockers.

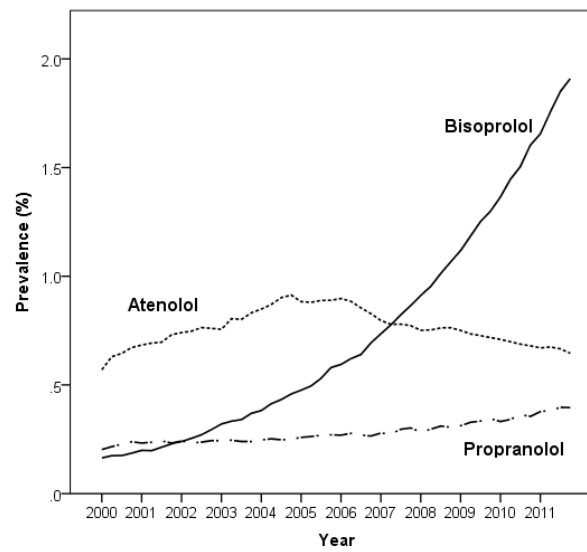


Figure 38b. Individual beta-blockers.

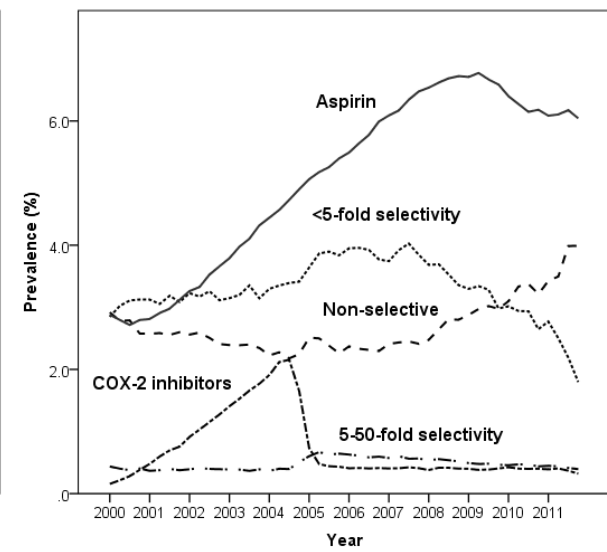


Figure 38c. Oral NSAIDs

Figure 38. Drug utilisation trends for oral beta-blockers and NSAIDs in patients from the active asthma cohort.

Oral NSAIDs

A total of 77424 patients from the active asthma cohort (27.5%, 95% CI 27.3 to 27.6) were prescribed 471706 oral NSAID prescriptions. Of these 77424 patients, 41033 patients (53.0%, 95% CI 52.7 to 53.4) were prescribed non-selective NSAIDs; 47938 patients (61.9%, 95% CI 61.6 to 62.3) were prescribed NSAIDs with <5-fold COX-2 selectivity; 4600 patients (5.9%, 95% CI 5.8 to 6.1) were prescribed NSAIDs with 5 to 50-fold COX-2 selectivity; and 8876 patients (11.5%, 95% CI 11.2 to 11.7) were prescribed COX-2 inhibitors. Of the 77424 patients prescribed an NSAID, 17378 patients were prescribed two classes of NSAID (22.5%, 95% CI 22.2 to 22.7), 3155 patients were prescribed three classes of NSAID (4.1%, 95% CI 3.9 to 4.2) and 460 patients were prescribed four classes of NSAIDs (0.6%, 95% CI 0.5 to 0.7) during follow up. Aspirin was prescribed to 19152 patients from the active asthma cohort (6.8%, 95% CI 6.7 to 6.9).

NSAIDs with <5-fold COX-2 selectivity (e.g. diclofenac) were the most frequently prescribed class of NSAID (44.3%), followed by non-selective NSAIDs (35.2%), COX-2 inhibitors (12.2%) and NSAIDs with 5 to 50-fold COX-2 selectivity (8.3%). Oral NSAID and aspirin prescribing varied significantly by age and gender (table 20). The number of NSAID prescriptions increased with age. People aged 60-69 years were issued the most number of prescriptions except for aspirin in which more prescriptions were issued to people aged 70 and over. Women were issued more NSAID prescriptions than men.

Table 20. Number of NSAID and aspirin prescriptions by age, gender and selectivity in patients with active asthma.

Variable	Non-selective No. (%)	<5-fold selective No. (%)	5-50-fold selective No. (%)	COX-2 inhibitor No. (%)	Aspirin No. (%)
Age group					
▪ 18-29	13869 (8.4)	16748 (8.0)	668 (1.7)	1245 (2.2)	1132 (0.3)
▪ 30-39	21980 (13.3)	28808 (13.8)	2093 (5.4)	4346 (7.5)	4986 (1.1)
▪ 40-49	32970 (19.9)	43490 (20.8)	6454 (16.5)	9491 (16.4)	25947 (5.6)
▪ 50-59	34253 (20.6)	45649 (21.9)	9982 (25.5)	13769 (23.9)	69645 (15.1)
▪ 60-69	36877 (22.2)	44100 (21.1)	11184 (28.6)	15206 (26.3)	139450 (30.2)
▪ ≥70	26084 (15.7)	30031 (14.4)	8745 (22.4)	13664 (23.7)	220592 (47.8)
Gender					
▪ Male	54237 (32.7)	68008 (32.6)	10630 (27.2)	13771 (23.9)	197481 (42.8)
▪ Female	111796 (67.3)	140818 (67.4)	28496 (72.8)	43950 (76.1)	264271 (57.2)
Total	166033 (100.0)	208826 (100.0)	39126 (100.0)	57721 (100.0)	461752 (100.0)

Percentages are column percentages.

The quarterly prevalence of oral NSAID and aspirin prescribing in people with active asthma is presented in figure 38c. Between the first quarter of 2000 and the last quarter of 2011, the quarterly prevalence of non-selective NSAID prescribing rose from 2.9% (95% CI 2.8 to 3.1) in the first quarter of 2000 to 4.0% (95% CI 3.9 to 4.1) in the last quarter of 2011, a significant relative rise of 36.6% (95% CI to 27.1 to 46.6) over the 12 year period. Although the quarterly prevalence of NSAID prescribing with <5 fold COX-2 selectivity fell from 2.9% (95% CI 2.7 to 3.0) in the first quarter of 2000 to 1.8% (95% CI 1.7 to 1.9) in the last quarter of 2011, a significant relative fall of 36.8% (95% CI to 28.8 to 45.3), prescribing initially increased and then started to fall in 2007. Between the first quarter of 2000 and the last quarter of 2011, the quarterly prevalence of NSAID prescribing with 5-50 fold COX-2 selectivity did not significantly change over the 12 year period (0.44% (95% CI 0.38 to 0.50) in the first quarter of 2000 compared to 0.39% (95% CI 0.35 to 0.44) in the last quarter of 2011.

Among each class, the most commonly prescribed drugs were: ibuprofen (61.7%) and naproxen (29.3%) for non-selective NSAIDs; diclofenac (90.0%) for NSAIDs with <5 fold COX-2 selectivity; meloxicam (75.0%) for NSAIDs with 5-50 fold COX-2 selectivity; and celecoxib (47.2%) for COX-2 inhibitors. The quarterly prevalence of ibuprofen prescribing fell from 2.1% (95% CI 2.0 to 2.2) in the first quarter of 2000 to 1.6% (95% CI 1.5 to 1.7) in the last quarter of 2011, a significant relative fall of 23.6% (95% CI 13.5 to 33.7) and absolute fall of 0.5% (95% CI 0.3 to 0.7). In comparison, the quarterly prevalence of naproxen prescribing rose from 0.5% (95% CI 0.5 to 0.6) in the first quarter of 2000 to 2.34% (95% CI 2.3 to 2.5) in the last quarter of 2011, a significant relative rise of 345% (95% CI 315.1 to 377.4) and absolute rise of 1.8% (95% CI 1.7 to 2.0). The quarterly prevalence of diclofenac prescribing fell from 2.4%

(95% CI 2.3 to 2.5) in the first quarter of 2000 to 1.5% (95% CI 1.5 to 1.6) in the last quarter of 2011, a significant relative fall of 35.7% (95% CI 26.5 to 45.0) and absolute fall of 0.9% (95% CI 0.6 to 1.1). The quarterly prevalence of meloxicam and celecoxib prescribing followed similar trends to those of the class effects. The quarterly prevalence of aspirin prescribing among patients with active asthma rose from 2.9% (95% CI 2.7 to 3.0) in the first quarter of 2000 to 6.0% (95% CI 5.6 to 6.2) in the last quarter of 2011, a significant relative rise of 109.7% (95% CI 99.0 to 120.5) and absolute rise of 3.2% (95% CI 2.9 to 3.5).

6.6.3 Drug utilisation studies - discussion

By the end of 2011, the prevalence of selective and non-selective beta-blocker prescribing had risen by around 200% and 87% respectively. Selective beta-blockers were prescribed more often to older patients more likely to have compelling indications for beta-blockade such as ischaemic heart disease and heart failure. My pilot work using Scottish electronic medical record data reported a prevalence of selective and non-selective beta-blocker prescribing of 1.7% and 1.1% respectively during 2005 and 2007 (84). For selective beta-blockers this remained similar (figure 38a) whereas non-selective beta-blockers prescribing was greater in my pilot work than observed here. This chapter demonstrates the rising pattern of oral beta-blocker prescribing, not apparent using a cross-sectional approach. During this time a switch in prescribing bisoprolol instead of atenolol occurred probably related to changing recommendations for the management of cardiovascular conditions during the study period.

There are three key points to note with regards to oral NSAID and aspirin prescribing over the study period. The first is the rise in non-selective NSAID use and fall in the use

of NSAIDs with less than 5-fold selectivity (which were similar in size). This was due to a rise in naproxen prescribing and a fall in diclofenac prescribing, probably related to emerging cardiovascular safety concerns associated with diclofenac. The second striking feature is the rise and rapid fall in COX-2 inhibitor prescribing which again relates to cardiovascular safety concerns, initially with rofecoxib which led to its voluntary withdrawal from the market in the second half of 2004 (216). Although celecoxib and etoricoxib are still available, COX-2 inhibitor prescribing in asthma is scarce despite their potential safety profile in AERD and in people with asthma with unknown AERD status as discussed in chapter 5. The last point to note is reversal of the increasing trend in aspirin prescribing possibly as a result of changing recommendations for routine use of aspirin for primary prevention of cardiovascular disease.

6.7 Summary

This chapter described the CPRD active asthma cohort, determined measures of disease frequency and assessed risk factors for asthma events to check data accuracy and representativeness. Overall, the demographics of people within the CPRD active asthma cohort appear representative of people with asthma, and known risk factors which modify the incidence of asthma exacerbations were reproduced in the nested case control study. This provides some reassurance as to the validity of CPRD data and increases confidence in the validity and generalisability of analyses evaluating the risk of beta-blockers and NSAIDs using the active asthma cohort. The majority of prescriptions for chronic conditions are issued through UK general practice and therefore the drug utilisation studies in this chapter are likely to be a valid representation of UK clinical practice which demonstrates that a suitable population at risk from beta-blockers and NSAIDs exists.

Chapter 7: Adverse Respiratory Effect of Propranolol in Asthma: Nested Case Control Study and Self-Controlled Case Series in People with Asthma and Anxiety

7.1 Introduction

Propranolol is a non-selective beta-blocker introduced into clinical practice for the management of cardiovascular disease. Propranolol improves exercise tolerance in people with angina pectoris by blunting catecholamine-induced increases in heart rate, blood pressure and myocardial contractility, thereby reducing myocardial oxygen consumption (217). Propranolol can be used to control atrial and ventricular arrhythmias with one study showing suppression of chronic ventricular arrhythmias in around 88% of people at a mean daily dose of 290 mg (218). Propranolol can also lower blood pressure in hypertensive patients and can improve survival following myocardial infarction with long term use by around 20% (74, 219). Over time, other selective and non-selective beta-blockers have been developed which are currently preferred for the management of cardiovascular disease instead of propranolol. However, propranolol is still commonly used for the management of several non-cardiac conditions including anxiety, migraine, benign essential tremor and the symptoms of thyrotoxicosis.

Anxiety is a common psychological condition associated with several comorbidities including asthma. The prevalence of anxiety disorder is greater in people with asthma compared to the general population and prevalence of anxiety disorder is thought to increase with increasing asthma severity (220). One US study involving over 2000 young people aged 16 to 21 years of age reported a 21% prevalence of anxiety disorder among people with asthma compared to 13.6% in people without, whilst another study reported significantly greater anxiety scores among people with treatment-resistant asthma compared to other people with asthma measured using the Hospital Anxiety Depression Scale (HADS) (221, 222).

Anxiety disorder is associated with a number of poor asthma outcomes including worse asthma-related quality of life scores, increased health care utilisation and cost, increased use of rescue medication and rates of asthma hospitalisation (220). In one UK study, asthma hospitalisation rates among people with current comorbid mood disorders (depression and anxiety) was 44.5 per 10,000 person years compared to 36.4 per 10,000 person years in those without (223).

Propranolol is prescribed for anxiety which is a confounder when investigating the risk of propranolol in people in asthma (220). Therefore comparing the risk of propranolol with other beta-blockers in a single analysis potentially leads to confounded estimates because any observed increase in asthma outcomes may be related to the presence or absence of anxiety between cases and controls rather than the drug per se (confounding by indication). The risk factor analysis conducted in chapter 6 found a significant association with PCAE and current anxiety but not with asthma hospitalisation or death. The drug utilisation studies presented in the same chapter highlighted an increasing prevalence of propranolol prescribing among people with asthma which demonstrates a population at risk.

7.2 Aim

The aim of this chapter was to assess the adverse respiratory effect of propranolol using linked electronic health data.

7.3 Methods

Primary analysis using the nested case control study

Population

The nested case control study measured the association between propranolol exposure and asthma events in a cohort of people with asthma and anxiety derived from the CPRD adult active asthma cohort (described in chapter 2, page 66). Entry into the asthma anxiety cohort occurred on or after the date of entry to the CPRD active asthma cohort. The asthma anxiety cohort consisted of people in the CPRD active asthma cohort who additionally had a Read code for anxiety disorder in their electronic medical record. Entry into the asthma anxiety cohort was defined as the date of entry into the CPRD active asthma cohort if a Read code for anxiety disorder was recorded within the previous year. Otherwise entry into the asthma anxiety cohort was defined as the date of the anxiety Read code if this occurred for the first time during the CPRD active asthma cohort follow-up. Therefore, this definition was more likely to include people with current anxiety disorders. Cohort follow-up remained unchanged as previously described (chapter 2, page 67). Analysis was restricted to people from practices linked to the HES and ONS databases providing full outcome ascertainment.

Case and control selection

Outcomes consisted of asthma death, asthma hospitalisation and PCAE as previously defined (chapter 2, page 67). For each outcome, up to 10 controls were randomly selected and matched to each case on age (categorised into deciles), gender, calendar year of cohort entry and whether patients were diagnosed with asthma before the age of 45 using incidence density sampling. When a case could not be matched to one or more controls, the matching process was repeated without age. This was a pragmatic decision

to include all cases affecting 2 cases (0.4%) of asthma hospitalisation and 12 cases (0.5%) of PCAE.

Exposures

Propranolol exposure was defined as current incident user, current prevalent user and non-user as described in the general methods chapter (chapter 2, page 72). Among current users, exposure to oral propranolol was evaluated by dose, stratified into low to moderate daily dose (≤ 80 mg) and high daily dose (> 80 mg). The association with propranolol was evaluated using three risk windows consisting of 30, 60 and 90 days.

Confounders and data analysis

Multiple imputation was used to impute missing data on height, weight and smoking status as previously described (chapter 2, page 75). For each analysis, adjustment was made for variables listed in table 21, according to clinical relevance and model fit (chapter 2, page 73). Chi-squared testing and analysis of variance (ANOVA) was used to determine statistically significant differences in patient characteristics. Conditional logistic regression was used to estimate odds ratios which provide unbiased estimates of the incidence rate ratio for the association between propranolol and asthma events.

Table 21. Confounders used for risk adjustment in the nested case control analysis between propranolol and asthma death, asthma hospitalisation and primary care asthma exacerbation.

Characteristic	Death	Hospitalisation	PCAE
Exact age [¥]	Yes	Yes	Yes
Deprivation [€]	Yes	Yes	Yes
Medications*			
▪ ICS	Yes	Yes	Yes
▪ LABA	Yes	Yes	Yes
▪ LABAICS	Yes	Yes	Yes
▪ Leukotriene antagonist	Yes	Yes	Yes
▪ Methylxanthine	Yes	Yes	Yes
▪ No. of SABA [¥]	Yes	Yes	Yes
▪ Oral steroid	Yes	Yes	No
▪ NSAIDs	Yes	Yes	Yes
Comorbidity			
▪ Nasal polyps	No	Yes	Yes
▪ BMI [¥]	Yes	Yes	Yes
▪ Charlson co-morbidity score [¥]	Yes	Yes	Yes
Smoking status	Yes	Yes	Yes
Previous asthma hospitalisation	Yes	Yes	Yes
RTI*	Yes	Yes	Yes
Asthma review ^δ	No	No	Yes

*= In the 90 days prior to index date. €= Index of multiple deprivation decile.

δ = In the 365 days prior to index date.

¥ = Continuous variable. PCAE = primary care asthma exacerbation.

Sensitivity analyses

The following sensitivity analyses were performed for asthma hospitalisation and PCAE to test the robustness of the results as previously described (chapter 2, page 76):

- excluding patients hospitalised during the risk period
- excluding patients over the age of 40 years who smoked
- excluding patients diagnosed with asthma over the age of 45
- excluding patients not matched in the first round of control selection (i.e. not matched on age, since this is the matching variable dropped in the second round)
- complete case analysis

Secondary analysis using the self-controlled case series

The SCCS method has previously described in chapter 2 (page 77). The SCCS was conducted over a 360 day study period centred on incident propranolol exposure (first prescription in the file in people with at least 1 year of follow up prior to the first prescription) as previously defined (chapter 2, page 77). The beginning of the observation period was defined as 180 days prior to the date of the incident propranolol prescription and the end of the observation period was defined as 180 days following this incident prescription. The SCCS was performed for PCAE as previously defined, using 30 day, 60 day and 90 day acute risk periods beginning on the incident prescription date for propranolol. Exposure beyond these risk windows was categorised as chronic exposure. A 30 day pre-risk period was used to account for short-lived event dependent exposures. All remaining person time was classed as baseline.

Confounders and data analysis

Time-varying exposure to the following medications issued within 90 day consecutive periods was adjusted for in the analysis as previously described (chapter2, page 81):

ICS; inhaled LABAs; leukotriene antagonists; methlyxanthines; and the total number of SABA prescriptions. Additional risk adjustment was also made for seasonal variation.

Crude and adjusted incidence rate ratios (IRR) were calculated using conditional

Poisson regression with analyses stratified by dose as previously defined (page 81).

7.4 Results

The asthma anxiety cohort consisted of 20093 patients with a mean age at cohort entry of 40.6 years (SD 15.4) and more women than men (71.8% vs. 28.2% respectively).

During follow-up of the asthma anxiety cohort, a total of 12 asthma deaths, 470 asthma hospitalisations and 1855 PCAE occurred. Propranolol was prescribed to 1039 patients (5.2%) in the asthma anxiety cohort during a mean of 2.9 years of follow-up.

7.4.1 Primary analysis using the nested case control study

Asthma death

All cases of asthma death were fully matched to 10 controls. Table 22 describes the characteristics of the 12 cases of asthma death matched to 120 controls. There were no significant differences in matching criteria between cases and controls. Cases died of asthma at a mean age of 53.4 years and were predominantly women (75.0%). Cases had a statistically significant higher use of oral steroids and SABAs in the 90 days prior to the index date. A greater proportion of cases were current smokers which was statistically significant. Cases had a lower mean BMI, were more likely to have previously been hospitalised for asthma and hospitalised for any cause within 90 days of the index date but were not statistically significant.

Table 22. Characteristics of cases and controls for asthma death in the propranolol analysis.

Characteristics	Cases N=12	Controls N=120	p-value
Matching variables			
Age (years, SD)	53.4 (13.5)	53.7 (12.9)	0.948*
Female gender	9 (75.0)	90 (75.0)	1.000
Years of follow-up to index date (years, SD)	2.4 (2.7)	2.4 (2.6)	0.983*
Diagnosed with asthma \leq age 45	7 (58.3)	70 (58.3)	1.000
Potential confounders			
Asthma therapy in the 90 days prior to index date			
▪ ICS	4 (33.3)	52 (43.3)	0.504
▪ LABA	1 (8.3)	7 (5.8)	1.000
▪ LABAICS	4 (33.3)	32 (26.7)	0.877
▪ Leukotriene antagonist	1 (8.3)	5 (4.2)	1.000
▪ Methylxanthine	2 (16.7)	3 (2.5)	0.097
▪ Oral steroid	7 (58.3)	11 (9.2)	0.000
▪ Mean no. of SABA prescriptions (SD)	2.3 (1.8)	1.4 (1.3)	0.028*
Comorbidity			
▪ Nasal polyps	0 (0.0)	1 (0.8)	1.000
▪ Mean BMI (SD)	23.8 (6.1)	28.4 (7.2)	0.068*
▪ Mean Charlson co-morbidity score (SD)	1.9 (1.2)	1.4 (0.9)	0.065*
Smoking status			
▪ Current smoker	7 (58.3)	35 (29.2)	0.039
▪ Ex-smoker	3 (25.0)	41 (34.2)	0.748
▪ Non-smoker	1 (8.3)	42 (35.0)	0.120
▪ Missing	1 (8.3)	2 (1.7)	
Previous hospitalisation for asthma	3 (25.0)	12 (10.0)	0.278
RTI recorded in the 90 days prior to index date	3 (25.0)	14 (11.7)	0.388
Hospitalisation in the 90 day risk window	3 (25.0)	13 (10.8)	0.332
Asthma review in the 365 days prior to index date	5 (41.7)	60 (50.0)	0.582

*Continuous variable analysed using ANOVA, otherwise variables are categorical analysed using the Chi-square test. SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection, BMI = Body mass index. Cases and controls matched on age category, gender, calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

Asthma hospitalisation

A total of 2 cases (0.4%) were included unmatched on age. Table 23 describes the characteristics of the 470 cases of asthma hospitalisation matched to 4679 controls. There were no significant differences in matching criteria between cases and controls. Cases were hospitalised for asthma at a mean age of 42.6 years and were predominantly women (78.5%). Cases had significantly higher use of all types of asthma medication apart from ICS. A higher proportion of cases had a respiratory tract infection recorded, had previously been hospitalised for asthma and had been hospitalised for any cause within 90 days of the index date. Cases had a higher mean BMI and a greater proportion of patients with nasal polyps. A greater number of cases were current smokers and had attended a primary care asthma review within a year of the index date.

Table 23. Characteristics of case and controls for asthma hospitalisation in the propranolol analysis.

Characteristics	Cases N=470	Controls N=4679	p-value
Matching variables			
Age (years, SD)	42.6 (15.4)	42.6 (15.4)	0.979*
Female gender	369 (78.5)	3675 (78.5)	1.000
Years of follow-up to index date (years, SD)	2.3 (2.5)	2.3 (2.5)	0.977*
Diagnosed with asthma \leq age 45	386 (82.1)	3845 (82.2)	0.979
Potential confounders			
Asthma therapy in the 90 days prior to index date			
▪ ICS	191 (40.6)	1803 (38.5)	0.372
▪ LABA	74 (15.7)	400 (8.5)	0.000
▪ LABAICS	166 (35.3)	982 (21.0)	0.000
▪ Leukotriene antagonist	52 (11.1)	147 (3.1)	0.000
▪ Methylxanthine	30 (6.4)	54 (1.2)	0.000
▪ Oral steroid	201 (42.8)	327 (7.0)	0.000
▪ Mean no. of SABA prescriptions (SD)	2.4 (2.2)	1.2 (1.4)	0.000*
Comorbidity			
▪ Nasal polyps	23 (4.9)	147 (3.1)	0.043
▪ Mean BMI (SD)	29.4 (7.3)	27.9 (6.8)	0.000*
▪ Mean Charlson co-morbidity score (SD)	1.4 (1.1)	1.3 (1.0)	0.697*
Smoking status			
▪ Current smoker	179 (38.1)	1496 (32.0)	0.007
▪ Ex-smoker	127 (27.0)	1390 (29.7)	0.223
▪ Non-smoker	150 (31.9)	1626 (34.8)	0.218
▪ Missing	14 (3.0)	167 (3.6)	
Previous hospitalisation for asthma	119 (25.3)	224 (4.8)	0.000
RTI recorded in the 90 days prior to index date	103 (21.9)	409 (8.7)	0.000
Hospitalisation in the 90 day risk window	62 (13.2)	344 (7.4)	0.000
Asthma review in the 365 days prior to index date	239 (50.9)	2085 (44.6)	0.009

*Continuous variable analysed using ANOVA, otherwise variables are categorical analysed using the Chi-square test.

SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection,

BMI = Body mass index. Cases and controls matched on age category, gender, calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

Primary care asthma exacerbations

A total of 12 cases (0.5%) were included unmatched on age. Table 24 describes the characteristics of the 2455 cases of PCAE matched to 23864 controls. There were small but statistically significant differences in mean age (44.3 vs. 43.6 years) but not on the other matching criteria. PCAEs occurred at a mean age of 44.3 years predominantly in women (75.8%). Cases had significantly greater use of all types of asthma medications. A higher proportion of cases had attended an asthma review in the previous year and had a respiratory tract infection recorded within 90 days of the index date. Cases had small but statistically significant differences in BMI and cases had a greater number of ex-smokers and fewer non-smokers.

Table 24. Characteristics of case and controls for primary care asthma exacerbations in the propranolol analysis.

Characteristics	Cases N=2455	Controls N=23864	p-value
Matching variables			
Age (years, SD)	44.3 (15.3)	43.6 (15.0)	0.027*
Female gender	1852 (75.8)	18133 (76.3)	0.554
Years of follow-up to index date (years, SD)	1.6 (2.2)	1.6 (2.2)	0.668*
Diagnosed with asthma \leq age 45	1851 (75.4)	18175 (76.2)	0.398
Potential confounders			
Asthma therapy in the 90 days prior to index date			
▪ ICS	1020 (41.8)	8836 (37.2)	0.000
▪ LABA	251 (10.3)	1228 (5.2)	0.000
▪ LABAICS	599 (24.5)	4083 (17.2)	0.000
▪ Leukotriene antagonist	78 (3.2)	386 (1.6)	0.000
▪ Methylxanthine	34 (1.4)	124 (0.5)	0.000
▪ Mean no. of SABA prescriptions (SD)	1.4 (1.4)	1.0 (1.2)	0.000*
Comorbidity			
▪ Nasal polyps	85 (3.5)	492 (2.1)	0.000
▪ Mean BMI (SD)	28.3 (6.7)	27.5 (6.7)	0.000*
▪ Mean Charlson co-morbidity score (SD)	1.4 (1.0)	1.4 (1.0)	0.894*
Smoking status			
▪ Current smoker	779 (31.9)	7225 (30.4)	0.133
▪ Ex-smoker	745 (30.5)	6614 (27.8)	0.006
▪ Non-smoker	842 (34.5)	8869 (37.3)	0.005
▪ Missing			
Previous hospitalisation for asthma	152 (6.2)	648 (2.7)	0.000
RTI recorded in the 90 days prior to index date	325 (13.3)	1517 (6.4)	0.000
Hospitalisation in the 90 day risk window	161 (6.6)	1571 (6.6)	0.964
Asthma review in the 365 days prior to index date	1236 (50.6)	10147 (42.7)	0.000

*Continuous variable analysed using ANOVA, otherwise variables are categorical analysed using the Chi-square test.

SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection, BMI = Body mass index. Cases and controls matched on age category, gender, calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

Propranolol exposure

The crude and adjusted associations between oral propranolol exposure and asthma events are shown in table 25. Due to low power for the 30 and 60 day risk windows, it was only possible to estimate the relative incidence for asthma death using the 90 day risk window for total and prevalent exposure. There was no significant difference found for all exposure in the 90 day risk window. It was not possible to estimate relative incidence for incident propranolol exposure. There was no significant difference found for prevalent propranolol exposure in the 90 day risk window.

Overall, there was no significant increase in the relative incidence of asthma hospitalisation or PCAE associated with any propranolol exposure (incident and prevalent combined) with any of the risk windows. When stratified by type of exposure, the relative incidence of asthma hospitalisation was significantly increased with incident propranolol exposure using a 30 day risk window (IRR 13.69 (95% CI 2.28 to 82.17) $p=0.004$) with relative incidence falling as the risk window increased.

No significant differences in PCAE were observed for incident propranolol exposure.

No significant increase in the relative incidence of asthma death, asthma hospitalisation or PCAE was observed with prevalent propranolol exposure.

Table 25. Crude and adjusted incidence rate ratios for the association between oral propranolol exposure and asthma events.

Risk window	Any				Incident				Prevalent			
	Crude IRR	Adjusted* IRR	95% CI	p-value	Crude IRR	Adjusted* IRR	95% CI	p-value	Crude IRR	Adjusted* IRR	95% CI	p-value
Death												
▪ 30 day	-	-	-	-	-	-	-	-	-	-	-	-
▪ 60 day	-	-	-	-	-	-	-	-	-	-	-	-
▪ 90 day	2.50	1.26	0.00-753.6	0.943	-	-	-	-	3.33	1.26	0.00-753.6	0.943
Hospitalisation												
▪ 30 day	1.39	2.29	0.77-6.78	0.135	5.00	13.69	2.28-82.17	0.004	0.93	1.22	0.30-4.97	0.785
▪ 60 day	1.18	1.54	0.57-4.20	0.399	1.54	2.78	0.53-14.58	0.226	1.05	1.21	0.35-4.21	0.763
▪ 90 day	0.97	1.16	0.44-3.07	0.762	1.30	1.79	0.44-7.30	0.415	0.77	0.84	0.22-3.27	0.803
PACAE												
▪ 30 day	0.77	0.80	0.49-1.28	0.349	0.19	0.25	0.03-1.81	0.169	0.97	0.97	0.60-1.57	0.889
▪ 60 day	0.88	0.91	0.62-1.33	0.619	0.43	0.50	0.18-1.38	0.182	1.04	1.03	0.69-1.55	0.872
▪ 90 day	0.84	0.86	0.61-1.23	0.415	0.51	0.57	0.27-1.24	0.157	1.01	0.99	0.66-1.48	0.956

*Adjustment for confounders listed in table 21 (page 190). Empty cells = inestimable due to lack of exposure in the risk window.

The association between oral propranolol exposure and asthma hospitalisation according to dose of exposure are shown in table 26. Overall, there was a significant increase in the relative incidence of asthma hospitalisation with any (incident and prevalent combined) high dose propranolol exposure. This was significant for each of the risk windows with relative incidence falling as the risk window increased in duration (IRR 7.98 (95% CI 1.82 to 35.02), IRR 7.90 (95% CI 1.88 to 33.24) and IRR 4.30 (95% CI 1.09 to 16.98) for the 30, 60 and 90 day risk window respectively).

When stratified by type of exposure, incident high dose propranolol exposure was associated with a larger significant increase in the relative incidence of asthma hospitalisation which was significant for all of the risk windows (IRR 13.37 (95% CI 1.08 to 165.97), IRR 13.70 (95% CI 1.46 to 128.46) and IRR 7.59 (95% CI 1.30 to 44.24) for the 30, 60 and 90 day risk window respectively). Incident low to moderate dose propranolol exposure was associated with a smaller significant increase in the relative incidence of asthma hospitalisation which was significant for the 30 day risk window only (IRR 11.13 (95% CI 1.03-119.89)).

Prevalent high dose propranolol exposure was associated with a non-significant increase in the relative incidence of asthma hospitalisation (IRR 5.84 (95% CI 0.93 to 36.88), IRR 5.08 (95% CI 0.67 to 38.71) and IRR 2.76 (95% CI 0.27 to 27.70) for the 30, 60 and 90 day risk window respectively).

Table 26. Crude and adjusted incidence rate ratios for the association between oral propranolol exposure and asthma events by dose.

Risk window	Any				Incident				Prevalent			
	Crude IRR	Adjusted* IRR	95% CI	p-value	Crude IRR	Adjusted* IRR	95% CI	p-value	Crude IRR	Adjusted* IRR	95% CI	p-value
High dose												
Hospitalisation												
▪ 30 day	3.00	7.98	1.82-35.02	0.006	5.00	13.37	1.08-165.97	0.044	2.50	5.84	0.93-36.88	0.060
▪ 60 day	3.64	7.90	1.88-33.24	0.005	6.67	13.70	1.46-128.26	0.022	2.50	5.08	0.67-38.71	0.117
▪ 90 day	2.67	4.30	1.09-16.98	0.037	4.29	7.59	1.30-44.24	0.024	1.25	2.76	0.27-27.70	0.389
PCAE												
▪ 30 day	1.66	1.50	0.57-3.94	0.415	1.23	1.50	0.18-12.68	0.986	1.82	1.50	0.51-4.45	0.656
▪ 60 day	1.19	1.15	0.48-2.72	0.759	1.49	1.77	0.51-6.13	0.367	1.00	0.85	0.26-2.82	0.787
▪ 90 day	0.99	0.94	0.40-2.21	0.891	1.37	1.57	0.54-4.55	0.411	0.64	0.53	0.13-2.25	0.391
Low to moderate dose												
Hospitalisation												
▪ 30 day	0.77	0.91	0.17-4.93	0.909	3.33	11.13	1.03-119.89	0.047	0.43	0.40	0.04-3.90	0.433
▪ 60 day	0.47	0.54	0.11-2.68	0.450	0.83	0.83	0.09-7.51	0.870	0.33	0.35	0.04-3.18	0.348
▪ 90 day	0.60	0.65	0.18-2.38	0.515	0.53	0.62	0.07-5.28	0.664	0.64	0.38	0.06-2.30	0.289
PCAE												
▪ 30 day	0.67	0.72	0.42-1.23	0.233	-	-	-	-	0.86	0.88	0.51-1.52	0.656
▪ 60 day	0.84	0.88	0.58-1.32	0.529	0.37	0.43	0.13-1.37	0.152	1.00	1.01	0.65-1.57	0.977
▪ 90 day	0.88	0.91	0.63-1.32	0.627	0.50	0.57	0.25-1.30	0.178	1.06	1.06	0.70-1.60	0.801

*Adjustment for confounders listed in table 21 (page 190). Empty cells = inestimable due to lack of exposure in the risk window.

The association between oral propranolol exposure and PCAE according to dose of exposure are shown in table 26. Overall, there was no significant increase in the relative incidence of PCAE with any (incident and prevalent combined) high or low to moderate dose propranolol exposure. When stratified by type of exposure, incident high dose exposure was not associated with an increase in the relative incidence of PCAE (IRR 1.50 (95% CI 0.18 to 12.68), IRR 1.77 (95% CI 0.51 to 6.13) and IRR 1.57 (95% CI 0.54 to 4.55) for the 30, 60 and 90 day risk window respectively). Incident low to moderate dose exposure was not associated with a significant increase in the relative incidence of PCAE. There was no significant increase in the relative incidence of PCAE associated with prevalent high dose or low to moderate dose propranolol exposure.

Nested case control sensitivity analyses

Results from sensitivity analyses for the two outcomes examined (asthma hospitalisation and PCAE) are presented for any propranolol exposure stratified by type of exposure and shown in table 27.

1. Excluding patients hospitalised within the risk period

This was done to assess any impact of immortal time bias. For asthma hospitalisation, this involved excluding 31 (6.6%), 55 (11.7%) and 62 (13.2%) of cases for the 30, 60 and 90 day risk windows respectively whilst for PCAE this involved excluding 64 (2.6%), 119 (4.9%) and 161 (6.6%) cases for the 30, 60 and 90 day risk windows respectively. This analysis produced very similar results to the main analysis (shown in table 25) with a significantly increased risk of asthma hospitalisation associated with incident propranolol exposure (IRR 13.78 (95% CI 2.28 to 83.12)) and no significant increase with any other type of exposure, risk window or event.

Table 27. Sensitivity analyses for the propranolol analysis as per methods.

	IRR	Any 95% CI	IRR	Incident 95% CI	IRR	Prevalent 95% CI
Hospitalised in risk window						
Hospitalisation						
30 day	1.78	0.53-6.00	13.78	2.28-83.12	0.71	0.12-3.99
60 day	1.33	0.43-4.05	3.05	0.56-16.56	0.88	0.20-3.78
90 day	1.06	0.36-3.12	2.01	0.48-8.45	0.56	0.10-3.08
PCAE						
30 day	0.79	0.48-1.30	0.26	0.04-1.89	0.96	0.58-1.61
60 day	0.96	0.65-1.42	0.56	0.20-1.56	1.09	0.71-1.66
90 day	0.91	0.63-1.32	0.65	0.30-1.41	1.03	0.68-1.57
Diagnosed with asthma ≥45						
Hospitalisation						
30 day	2.14	0.62-7.37	18.62	2.72-127.35	0.82	0.14-4.74
60 day	1.46	0.47-1.04	2.90	0.55-15.44	1.02	0.23-4.50
90 day	1.12	0.38-3.31	1.80	0.44-7.34	0.66	0.12-3.64
PCAE						
30 day	0.91	0.52-1.59	0.34	0.05-2.52	1.13	0.64-2.00
60 day	1.01	0.65-1.55	0.47	0.15-1.52	1.21	0.76-1.92
90 day	0.89	0.59-1.35	0.49	0.20-1.22	1.11	0.70-1.77
Smokers over 40 years						
Hospitalisation						
30 day	1.88	0.44-7.99	8.57	0.77-95.17	1.12	0.18-6.99
60 day	0.87	0.23-3.29	0.57	0.24-5.12	1.10	0.24-5.12
90 day	0.71	0.20-1.03	0.65	0.11-4.01	0.77	0.13-4.47
PCAE						
30 day	0.79	0.46-1.35	-	-	0.96	0.55-1.66
60 day	0.95	0.63-1.45	0.46	0.14-1.48	1.12	0.72-1.75
90 day	0.90	0.61-1.32	0.59	0.26-1.36	1.04	0.67-1.61
Unmatched on age						
Hospitalisation						
30 day	2.31	0.78-6.86	14.04	2.33-84.66	1.22	0.30-5.03
60 day	1.55	0.57-2.45	2.86	0.54-15.03	1.21	0.35-4.23
90 day	1.17	0.44-3.10	1.82	0.45-7.41	0.84	0.22-3.28
PCAE						
30 day	0.80	0.50-1.30	0.25	0.03-1.79	0.98	0.60-1.59
60 day	0.91	0.63-1.33	0.50	0.18-1.38	1.04	0.69-1.56
90 day	0.86	0.61-1.23	0.57	0.27-1.24	0.99	0.66-1.48
Complete case analysis						
Hospitalisation						
30 day	2.37	0.78-7.18	16.91	2.36-120.95	1.23	0.30-5.17
60 day	1.66	0.59-4.65	4.42	0.79-24.72	1.22	0.34-4.34
90 day	1.24	0.46-3.37	2.31	0.52-10.19	0.83	0.21-3.27
PCAE						
30 day	0.83	0.51-1.37	0.35	0.05-2.58	0.97	0.59-1.59
60 day	0.92	0.62-1.36	0.62	0.22-1.73	1.00	0.65-1.53
90 day	0.90	0.62-1.30	0.60	0.26-1.39	1.01	0.67-1.52

Sensitivity analyses excluding patients: hospitalised within the risk window; smokers >40 years of age; diagnosed with asthma >45 years of age; unmatched on age; complete case analysis. IRR=incidence rate ratio.

2. *Excluding patients diagnosed with asthma over the age of 45 years*

This was done to assess any impact of including patients who may have unknown fixed airway obstruction. For asthma hospitalisation, this involved excluding 84 (17.9%) of cases whilst for PCAE this involved excluding 604 (24.6%) of cases. The significant association with incident propranolol exposure and asthma hospitalisation was larger than in the main analysis (IRR 18.62 (95% CI 2.72 to 127.35)) and less precise (having larger confidence intervals). There was no significant increase with any other type of exposure, risk window or event as per the main analysis.

3. *Excluding patients over the age of 40 years who smoked*

This was done to again assess any impact of including patients who may have unknown fixed airway obstruction. For asthma hospitalisation, this involved excluding 65 (13.8%) of cases whilst for PCAE this involved excluding 324 (13.2%) of cases. This analysis produced a non-significant association between incident propranolol exposure and asthma hospitalisation although effect estimates were large and in a similar direction (IRR 8.57 (95% CI 0.77 to 95.17)) whilst other results remained similar.

4. *Excluding patients originally unmatched on age*

This was done to assess for any residual confounding by age. For asthma hospitalisation, this involved excluding 2 (0.4%) of cases whilst for PCAE this involved excluding 12 (0.5%) of cases. This analysis produced very similar results the main analysis (shown in table 8.6) with a significantly increased risk of asthma hospitalisation associated with incident propranolol exposure (IRR 14.04 (95% CI 2.33 to 84.66)) and no significant increase with any other type of exposure, risk window or event.

5. *Complete case analysis*

This was done to assess the impact of multiply imputing data on height, weight and smoking status. For asthma hospitalisation, data was missing on height, weight and smoking status for 226 (4.4%), 172 (3.3%) and 181 (3.5%) of people respectively whilst for PCAE data was missing on height, weight and smoking status for 1062 (4.0%), 920 (3.5%) and 1125 (4.3%) of people respectively. Again this analysis produced very similar results the main analysis with a significantly increased risk of asthma hospitalisation associated with incident propranolol exposure (IRR 16.91 (95% CI 2.36 to 120.95)) and no significant increase with any other type of exposure, risk window or event.

8.4.2 Secondary analysis using the self-controlled case series

The SCCS consisted of 99 patients (mean age 42 years, 86% female) from the CPRD active asthma cohort with incident propranolol exposure and a total of 121 PCAEs. The number of events, total person time and crude incidence of PCAE for the baseline period, the pre-risk period, the acute risk period and the chronic risk period is shown in table 29. As expected, the crude incidence of PCAE was lower during the pre-risk period (17.3 per 10,000 person days). The crude incidence of PCAE was greater during the acute risk period compared to baseline for the 30 and 90 day risk windows only (40.8 vs. 34.2, and 38.3 vs. 34.8 per 10,000 person days for the 30 and 90 day acute risk windows respectively).

The crude and adjusted relative incidence of PCAE for each risk period and dose is shown in table 29. Overall, the relative incidence of PCAE was not significantly increased with any propranolol exposure (high and low dose combined) (IRR 1.15 (95%

CI 0.62 to 2.13), IRR 0.89 (95% CI 0.53 to 1.48) and IRR 1.03 (95% CI 0.67 to 1.59) for the 30, 60 and 90 day acute risk windows respectively). There was no significant increase in the relative incidence of PCAE with any chronic propranolol exposure.

When stratified by dose, no significant increase in the relative incidence of PCAE occurred with either high dose or low to moderate dose propranolol exposure although relative incidences were generally higher for acute high dose exposure compared to low to moderate dose exposure.

The relative incidence of PCAE was increased among all risk periods for chronic high dose propranolol exposure but was not statistically significant (IRR 2.63 (95% CI 0.35 to 20.05), IRR 3.95 (95% CI 0.50 to 31.03) and IRR 3.01 (95% CI 0.24 to 37.94) respectively). No significant increase in relative incidence of PCAE with low to moderate dose propranolol occurred and relative incidences were smaller than with high dose exposure.

Table 28. Number of events, person time and crude incidence rates according to exposure group and risk window used in the propranolol self-controlled case series.

Risk Period	Events	Person time (Days)	Crude Incidence*
30 day			
▪ Pre-risk	5	2888	17.31
▪ Baseline	87	25460	34.17
▪ Acute	12	2944	40.76
▪ Chronic	17	3950	43.04
60 day			
▪ Pre-risk	5	2888	17.31
▪ Baseline	84	23658	35.51
▪ Acute	20	5910	33.84
▪ Chronic	12	2785	43.09
90 day			
▪ Pre-risk	5	2888	17.31
▪ Baseline	75	21562	34.78
▪ Acute	34	8876	38.31
▪ Chronic	7	1914	36.57

*Per 10,000 person days.

Table 29. Adjusted incidence rate ratios for propranolol exposure and primary care asthma exacerbations according to exposure group and dose range used in the self-controlled case series.

		Any			High dose			Low to moderate dose		
Risk Period	IRR	95% CI	p-value	IRR	95% CI	p-value	IRR	95% CI	p-value	
30 day										
▪ Baseline	1.00	-	-	1.00	-	-	1.00	-	-	
▪ Acute	1.15	0.62-2.13	0.664	1.81	0.47-7.02	0.389	1.01	0.70-1.46	0.964	
▪ Chronic	1.43	0.73-2.76	0.289	2.63	0.35-20.05	0.350	0.76	0.56-1.05	0.096	
60 day										
▪ Baseline	1.00	-	-	1.00	-	-	1.00	-	-	
▪ Acute	0.89	0.53-1.48	0.643	1.10	0.31-3.96	0.881	0.82	0.60-1.11	0.190	
▪ Chronic	1.34	0.56-3.21	0.513	3.95	0.50-31.03	0.193	0.75	0.52-1.06	0.100	
90 day										
▪ Baseline	1.00	-	-	1.00	-	-	1.00	-	-	
▪ Acute	1.03	0.67-1.59	0.899	1.45	0.43-4.92	0.552	0.81	0.62-1.07	0.132	
▪ Chronic	0.99	0.34-2.90	0.985	3.01	0.24-37.94	0.394	0.84	0.57-1.24	0.381	

*Adjusted for use of SABA, LABA, ICS, leukotriene receptor antagonists, methylxanthines and seasonal variation.

7.5 Discussion

This study investigated the association between propranolol exposure and asthma death, hospitalisation and PCAE. The primary analysis was the nested case control study which found a 13-fold increased risk of asthma hospitalisation associated with incident propranolol exposure and an 8-fold increased risk associated with high dose propranolol exposure. Although effect estimates for the association between asthma hospitalisation and prevalent high dose propranolol exposure were increased, they did not reach statistical significance. There was also a significant 11-fold increased risk of asthma hospitalisation associated with low to moderate incident propranolol exposure using the 30 day risk period only.

In the nested case control study and the SCCS, there was no significant increase in PCAE associated with any type of propranolol exposure although effect estimates were generally larger for incident high dose exposure. Similar to the nested case control study, chronic high-dose propranolol exposure was associated with a larger but non-significant increased risk in PCAE in the SCCS. Similar to the nested case control study, low to moderate propranolol exposure was not associated with a significant increase in PCAE in the SCCS.

The risk of asthma hospitalisation and PCAE in this study appeared to be in keeping with a dose response relationship to propranolol. The meta-analysis conducted in chapter 3 found that acute exposure to non-selective beta-blockers caused respiratory symptoms in around one in 13 people, falls in FEV1 of 20% or greater in around one in 8 people and a mean fall in FEV1 of around 11% in people with stable mild to moderate asthma. However when examining heterogeneity in response, propranolol was shown to

produce a greater mean fall in FEV1 of around 17% following single dose exposure suggesting that propranolol exposure may be riskier than other non-selective beta-blockers. The results from this chapter also suggest that risk from propranolol exposure in asthma appears to differ according to duration of administration with risk being greatest within the first 30 days of propranolol being prescribed.

Strengths and limitations

It was not possible to properly evaluate the risk of asthma death due to a lack of power and effect estimates often had wide confidence intervals demonstrating a lack of precision. The large number of calculations performed may increase the likelihood of a spuriously statistically significant association as a result of repeat testing. The nested case control study was conducted using a cohort of people with active asthma and anxiety in order to minimise confounding by indication. Although defining the study in this way may help to address confounding by indication in a between-person design, people with active anxiety may have higher levels of circulating endogenous catecholamines influencing airway smooth muscle tone potentially making beta-blockers more risky. People with asthma appear to have been prescribed propranolol for anxiety despite it being a known contraindication and the exact reason for this is unknown. It could be that propranolol was prescribed for symptoms which the clinician attributed to anxiety but were in fact symptoms relating to uncontrolled asthma and this population would be at greater risk of an adverse respiratory event from beta-blocker exposure. Conversely, propranolol may have been prescribed to people with less severe asthma and risk may conceivably be greater in people with more severe asthma.

The results from this chapter suggest that risk from propranolol exposure in asthma also appears to differ according to duration of administration with risk being greatest within the first 30 days of exposure. This may be similar to the effects of beta-blockers in heart failure, where acute beta-blocker exposure reduces myocardial contractility whilst chronic exposure is well tolerated and leads to beta-adrenoceptor up-regulation with beneficial effects on ejection fraction and survival. This is discussed in further detail in chapter 10. However, the duration of exposure required to develop any potential adaptive response is uncertain and could depend upon a number of factors including individual response. For this reason, differing durations of risk window were used to evaluate risk and as expected the greatest risk occurred shortly following propranolol initiation. This risk reduction as treatment duration increases could also be due to susceptible people with asthma developing adverse respiratory events from propranolol at the start of therapy and propranolol therapy then being discontinued. This population would then not go on to experience chronic exposure introducing potential selection bias.

The nested case control study was considered the primary analysis in this chapter with the SCCS the secondary analysis in an attempt to validate the results. The nested case control study is a between-person design whilst the SCCS is a within-person design. Although observational studies may suffer from bias and residual confounding, the approaches taken in this chapter were chosen to minimize this and be complementary because these two methods potentially suffer from different biases and confounding. The SCCS did not demonstrate an increased risk of PCAE in keeping with the nested case control study.

Acute risk periods in this SCCS analysis were based upon duration of time following an incident propranolol prescription and not upon known propranolol exposure in terms of when the drug was dispensed or when the patient actually took the drug. As such, exposure may have ended before the 60 and 90 day acute risk periods in some individuals potentially underestimating the relative incidence of PCAE. This was chosen: first to better compare with the nested case control study results; second because dosing instructions for propranolol were sometimes poorly defined (e.g. one tablet four times a day if required); and third because the date of incident propranolol exposure was determined by the prescription date which was used as a proxy for exposure. It is therefore unknown whether patients had this medication dispensed or when patients actually took propranolol for the first time. It was also unknown how compliant patients were to their medication regimes, but propranolol for anxiety is frequently taken as required rather than as a fixed daily dose making interpretation of dose instructions problematic.

Although the SCCS controls for all time-fixed confounders, time-varying confounders still need to be controlled for. The most common form of time-varying confounding used in the SCCS literature is age. For this SCCS analysis which was conducted over a period of one year, age is unlikely to be a strong time-varying confounder given the nature of adult asthma and when age was included in the analysis, it had had no significant impact on the effect estimate. In contrast, a standard approach using a longer study period (e.g. 12 years) may have created significant problems in controlling for time-varying confounding first in relation to propranolol exposure, and second in relation to changing asthma medication exposure and seasonal variation. It is likely that age would be a strong time-varying confounder if a longer study period was used. For

this reason, the SCCS design was centred on incident propranolol exposure from which the acute risk period (which was of most interest) could be evaluated.

7.6 Summary

This study demonstrated an increased risk of asthma hospitalisation among people with asthma with incident and high dose propranolol exposure in keeping with biological plausibility. This increased risk was shown using the nested case control study and no statistically significant increase in relative incidence of PCAE was seen although effect estimates were generally larger for incident high dose exposure. This inconsistency in results could be as a result of unmeasured confounding and/or the fact that propranolol tends to cause more severe reactions in susceptible people with asthma and anxiety who are possibly more likely to present in secondary care.

Insufficient power meant it was not possible to provide estimates for the association with asthma death. The following two chapters will evaluate oral beta-blockers commonly used for the management of cardiovascular disease and NSAIDs using a similar approach. The discussion section in chapter 10 will provide further detail and a comparison of these results with other chapters.

Chapter 8: Adverse Respiratory Effect of Cardiovascular Beta-Blockers in Asthma: Nested Case Control Study and Self-Controlled Case Series in People with Asthma and Cardiovascular Disease

8.1 Introduction

The previous chapter evaluated exposure to propranolol in a subcohort of patients with active asthma and anxiety in an attempt to address confounding by indication. This analysis demonstrated an increased risk of asthma hospitalisation related to incident high dose propranolol exposure. Propranolol is rarely used for the management of cardiovascular (CVS) disease in the UK, having been replaced by newer non-selective and selective beta-blockers which demonstrate similar CVS effects in relation to blunting catecholamine-induced increases in heart rate, blood pressure and myocardial contractility (217). In addition, labetalol is a non-selective beta-blocker mainly used for the management of pregnancy-induced hypertension. Despite the potential benefit of beta-blockers in people with cardiovascular disease (CVD), a European consensus statement recommended that all beta-blockers should be contraindicated in people with a history of asthma over concerns they may induce bronchospasm (224).

The meta-analysis of randomised blinded placebo-controlled trials presented in chapter 3 demonstrated that selective beta-blockers were much better tolerated than non-selective agents. However, they caused small mean falls in FEV1 of around 7%, significant falls in FEV1 of 20% or greater affecting around one in 8 people and a non-significant increase in symptoms affecting one in 33 people suggesting that selective beta-blockers still have a small but significant risk among people with asthma. Although these clinical trials may have strong internal validity, it is uncertain how generalizable these findings are because these trials consist of selected people with stable mild-to-moderate asthma who received close medical supervision that is not routinely available in the community setting. This is especially important given the drug utilisation study presented in chapter 6 highlighted an increasing prevalence of beta-blocker prescribing

among people with asthma clearly demonstrating a population at risk. Similar to the previous chapter, the incidence of asthma events is greater in people cardiovascular disease (47).

8.2 Aim

The aim of this chapter was to assess the adverse respiratory effect of oral beta-blockers commonly used for the management of CVD using linked electronic health data.

8.3 Methods

Primary analysis using the nested case control study

Population

The nested case control study measured the association between oral beta-blocker exposure (excluding propranolol and labetalol because these are indicated for other conditions as previously described) and asthma events in a cohort of people with asthma and CVD derived from the CPRD adult active asthma cohort (chapter 2, page 66). Entry into the asthma CVD cohort occurred on or after the date of entry to the CPRD active asthma cohort. The asthma CVD cohort consisted of people in the CPRD active asthma cohort who additionally had a Read code for CVD (ischaemic heart disease, chronic heart failure, cardiac arrhythmia, cerebrovascular disease, peripheral vascular disease or hypertension) ever recorded in their electronic medical record, AND who were prescribed one or more prescriptions for a CVS medication during their period of cohort follow-up. Exposure to CVS medication was defined by prescriptions for oral beta-blockers (excluding patients prescribed propranolol and labetalol), calcium channel blockers, diuretics, renin-angiotensin-system inhibitors, nitrates and doxazosin. Therefore, this definition included people with actively managed CVD.

Entry into the asthma CVD cohort was defined as the date of the first CVS medication prescribed on or after entry into the CPRD active asthma cohort. Cohort follow-up remained unchanged as previously described (chapter 2, page 67) but the asthma CVD cohort was additionally censored at the end of exposure to CVS medication (defined below). In circumstances when exposure to CVS medication ceased before the end of follow-up, end of exposure was determined as the date of the last CVS prescription with the addition of a 90 day grace period. Additionally, in circumstances where there were gaps between CVS prescriptions of greater than 180 days, cohort follow-up was censored using the prescription date immediately preceding the gap with the addition of a 90 day grace period. Analysis was restricted to people from practices which were linked to the HES and ONS databases providing full outcome ascertainment.

Case and control selection

Outcomes consisted of asthma death, asthma hospitalisation and PCAE as previously defined (chapter 2, pages 67). For each outcome, up to 10 controls were randomly selected and matched to each case on age (categorised into deciles), gender, calendar year of cohort entry and whether patients were diagnosed with asthma before the age of 45 using incidence density sampling. When a case could not be matched to one or more controls, the matching process was repeated without age. This was a pragmatic decision to include all cases and affected 2 cases (0.3%) of asthma hospitalisation and 8 cases (0.2%) of PCAE.

Exposures

Oral beta-blocker exposure was defined as current incident user, current prevalent user and non-user as described in the general methods chapter (page 72). Among current users, exposure to oral beta-blockers was evaluated by selectivity and dose. Dose was stratified into low to moderate daily dose and high daily dose as defined in chapter 2 (page 72). Oral beta-blocker exposure was evaluated using three risk windows consisting of 30, 60 and 90 days.

Confounders and data analysis

Multiple imputation was used to impute missing data on height, weight and smoking status as previously described (chapter 2, page 75). For each analysis, adjustment was made for the confounders listed in table 30 according to clinical relevance and model fit as previously described (chapter 2, page 73). Chi-squared testing and analysis of variance (ANOVA) was used to determine statistically significant differences in patient characteristics between cases and controls. Conditional logistic regression was used to estimate odds ratios which provide unbiased estimates of the incidence rate ratio for the association between oral beta-blockers and asthma events.

Sensitivity analyses

The following sensitivity analyses were performed for asthma hospitalisation and PCAE to test the robustness of the results as previously described (chapter 2, page 76):

- excluding patients hospitalised during the risk period
- excluding patients over the age of 40 years who smoked
- excluding patients diagnosed with asthma over the age of 45

Table 30. Confounders used for risk adjustment in the analysis between oral beta-blockers and asthma death, asthma hospitalisation and primary care asthma exacerbation.

Characteristic	Death	Hospitalisation	PCAE
Exact age [¥]	Yes	Yes	Yes
Deprivation [€]	Yes	Yes	Yes
Medications*			
▪ ICS	Yes	Yes	Yes
▪ LABA	Yes	Yes	Yes
▪ LABAICS	Yes	Yes	Yes
▪ Leukotriene antagonist	Yes	Yes	Yes
▪ Methylxanthine	Yes	Yes	Yes
▪ No. of SABA [¥]	Yes	Yes	Yes
▪ Oral steroid	Yes	Yes	No
▪ NSAIDs	Yes	Yes	Yes
Comorbidity			
▪ Nasal polyps	No	Yes	Yes
▪ BMI [¥]	Yes	Yes	Yes
▪ Charlson co-morbidity score [¥]	Yes	Yes	Yes
Smoking status	Yes	Yes	Yes
Previous asthma hospitalisation	Yes	Yes	Yes
RTI*	Yes	Yes	Yes
Asthma review ^δ	No	No	Yes

*= In the 90 days prior to index date. €= Index of multiple deprivation decile.

δ = In the 365 days prior to index date.

¥ = Continuous variable. PCAE = primary care asthma exacerbation.

- excluding patients not matched in the first round of control selection (i.e. not matched on age, since this is the matching variable dropped in the second round)
- complete case analysis

Secondary analysis using the self-controlled case series

The SCCS method has previously defined in chapter 2 (page 77). The SCCS was conducted over a 360 day study period centred on incident oral beta-blocker exposure (first prescription in the file in people with at least 1 year of follow up prior to the first prescription) as previously defined (chapter 2, page 77). The beginning of the observation period was defined as 180 days prior to the date of the incident oral beta-blocker prescription and the end of the observation period was defined as 180 days following this incident prescription. The SCCS was performed for PCAE as previously defined, using 30 day, 60 day and 90 day acute risk periods beginning on the incident prescription date for oral beta-blocker. Exposure beyond these risk windows was categorised as chronic exposure. A 30 day pre-risk period was used to account for short-lived event dependent exposures. All remaining person time was classed as baseline.

Confounders and data analysis

Time-varying exposure to the following medications issued within each 90 day consecutive period was then adjusted for in the analysis as previously described (chapter 2, page 80): ICS; inhaled LABAs; leukotriene antagonists; methylxanthines; and the total number of SABA prescriptions. Additional risk adjustment was also made for seasonal variation. Crude and adjusted incidence rate ratios (IRR) were calculated using conditional Poisson regression with analyses stratified by dose as previously defined (page 81).

8.4 Results

The asthma CVD cohort consisted of 35502 patients with a mean age at cohort entry of 60.1 years (SD 11.8) and more women than men (59.7% vs. 40.3% respectively).

During follow-up of the asthma CVD cohort, a total of 26 asthma deaths, 585 asthma hospitalisations and 4234 PCAE occurred. Selective beta-blockers were prescribed to 5017 patients (14.1%) and non-selective beta-blockers were prescribed to 407 patients (1.2%) in the asthma CVD cohort during a mean of 3.5 years of follow-up.

8.4.1 Primary analysis using the nested case control study

Asthma death

All cases of asthma death were matched to 10 controls. Table 31 describes characteristics of the 26 cases of asthma death compared to the 260 matched controls. There were no statistically significant differences in matching criteria between cases and controls. Cases died of asthma at a mean age of 71.7 years and were predominantly women (76.9%). Cases had a statistically significant higher use of SABAs and oral steroids within 90 days of the index date. Cases were more likely to have previously been hospitalised for asthma and hospitalised for any cause within 90 days of the index date which was statistically significant.

Table 31. Characteristics of cases and controls for asthma death in the cardiovascular beta-blocker analysis.

Characteristics	Cases N=26	Controls N=260	p-value
Matching variables			
Age (years, SD)	71.7 (15.2)	70.3 (14.1)	0.631*
Female gender	20 (76.9)	200 (76.9)	1.000
Years of follow-up to index date (years, SD)	4.1 (3.7)	4.0 (3.6)	0.872*
Diagnosed with asthma \leq age 45	6 (23.1)	60 (23.1)	1.000
Potential confounders			
Asthma therapy in the 90 days prior to index date			
▪ ICS	14 (53.8)	142 (54.6)	0.940
▪ LABA	4 (15.4)	29 (11.2)	0.520
▪ LABAICS	4 (15.4)	58 (22.3)	0.517
▪ Leukotriene antagonist	2 (7.7)	12 (4.6)	0.828
▪ Methylxanthine	2 (7.7)	4 (1.5)	0.171
▪ Mean no. of SABA prescriptions (SD)	2.7 (2.9)	1.3 (1.6)	0.000*
▪ Oral steroid	9 (34.6)	20 (7.7)	0.000
Comorbidity			
▪ Nasal polyps	2 (7.7)	14 (5.4)	0.968
▪ Mean BMI (SD)	27.8 (5.8)	29.3 (6.1)	0.260*
▪ Mean Charlson co-morbidity score (SD)	2.2 (1.1)	2.3 (1.8)	0.740*
Smoking status			
▪ Current smoker	4 (15.4)	20 (7.7)	0.328
▪ Ex-smoker	10 (38.5)	106 (40.8)	0.819
▪ Non-smoker	8 (30.8)	125 (48.1)	0.092
▪ Missing	4 (15.4)	9 (3.5)	
Previous hospitalisation for asthma	4 (15.4)	10 (3.8)	0.034
RTI recorded in the 90 days prior to index date	4 (15.4)	16 (6.2)	0.175
Hospitalisation in the 90 days prior to index date	13 (50.0)	18 (6.9)	0.000
Asthma review in the 365 days prior to index date	11 (42.3)	119 (45.8)	0.735

*Continuous variable analysed using ANOVA, otherwise variables are categorical analysed using the Chi-square test.

SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection, BMI = Body mass index. Cases and controls matched on age category, gender, calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

Asthma hospitalisation

A total of two cases (0.3%) were included unmatched on age. Table 32 describes the characteristics of the 585 cases of asthma hospitalisation matched to 5818 controls.

There were no significant differences in matching criteria between cases and controls.

Cases were hospitalised for asthma at a mean age of 62.0 years and were predominantly women (70.3%). Cases had a statistically significant higher use of all types of asthma medication. A significantly higher proportion of cases had a respiratory tract infection recorded, had previously been hospitalised for asthma and had been hospitalised for any cause within 90 days of the index date. Cases had small but statistically significant greater mean BMI and Charlson comorbidity score, and had fewer ex-smokers.

Table 32. Characteristics of case and controls for asthma hospitalisation in the cardiovascular beta-blocker analysis.

Characteristics	Cases N=585	Controls N=5818	p-value
Matching variables			
Age (years, SD)	62.0 (13.1)	62.2 (13.1)	0.760*
Female gender	411 (70.3)	4091 (70.3)	0.976
Years of follow-up to index date (years, SD)	2.8 (2.9)	2.8 (2.9)	0.975*
Diagnosed with asthma \leq age 45	197 (33.7)	1952 (33.6)	0.952
Potential confounders			
Asthma therapy in the 90 days prior to index date			
▪ ICS	259 (44.3)	2861 (49.2)	0.024
▪ LABA	115 (19.7)	532 (9.1)	0.000
▪ LABAICS	218 (37.3)	1296 (22.3)	0.000
▪ Leukotriene antagonist	66 (11.3)	182 (3.1)	0.000
▪ Methylxanthine	50 (8.5)	100 (1.7)	0.000
▪ Mean no. of SABA prescriptions (SD)	2.0 (1.7)	1.1 (1.3)	0.000*
▪ Oral steroid	264 (45.1)	400 (6.9)	0.000
Comorbidity			
▪ Nasal polyps	32 (5.5)	309 (5.3)	0.870
▪ Mean BMI (SD)	31.1 (7.0)	30.1 (6.3)	0.001*
▪ Mean Charlson co-morbidity score (SD)	2.0 (1.6)	1.9 (1.4)	0.018*
Smoking status			
▪ Current smoker	59 (10.1)	551 (9.5)	0.629
▪ Ex-smoker	220 (37.6)	2495 (42.9)	0.014
▪ Non-smoker	281 (48.0)	2611 (44.9)	0.144
▪ Missing	25 (4.3)	161 (2.8)	
Previous hospitalisation for asthma	83 (14.2)	111 (1.9)	0.000
RTI recorded in the 90 days prior to index date	106 (18.1)	384 (6.6)	0.000
Hospitalisation in the 90 days prior to index date	80 (13.7)	449 (7.7)	0.000
Asthma review in the 365 days prior to index date	273 (46.7)	2803 (48.2)	0.486

*Continuous variable analysed using ANOVA, otherwise variables are categorical analysed using the Chi-square test.

SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection, BMI = Body mass index. Cases and controls matched on age category, gender, calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

Primary care asthma exacerbations

Eight cases (0.2%) were included unmatched on age. Table 33 describes the characteristics of the 4234 cases of PCAE matched to 41881 controls. There were no significant differences in matching criteria between cases and controls. PCAEs occurred at a mean age of 62.8 years predominantly in women (66.5%). Cases had statistically significant greater use asthma medications apart from ICS. A significantly higher proportion of cases had attended an asthma review in the previous year, had a respiratory tract infection recorded within 90 days of the index date and had previously been hospitalised for asthma. Cases had a small but statistically significant increase in mean BMI, decrease in Charlson comorbidity score and increase in the proportion of patients with nasal polyps.

Table 33. Characteristics of case and controls for primary care asthma exacerbations in the cardiovascular beta-blocker analysis.

Characteristics	Cases N=4234	Controls N=41881	p-value
Matching variables			
Age (years, SD)	62.8 (11.8)	62.9 (11.7)	0.333*
Female gender	2815 (66.5)	27898 (66.6)	0.867
Years of follow-up to index date (years, SD)	2.0 (2.5)	2.0 (2.5)	0.988*
Diagnosed with asthma \leq age 45	1131 (26.7)	10932 (26.1)	0.390
Potential confounders			
Asthma therapy in the 90 days prior to index date			
▪ ICS	2074 (49.0)	19995 (47.7)	0.123
▪ LABA	421 (9.9)	2734 (6.5)	0.000
▪ LABAICS	986 (23.3)	7241 (17.3)	0.000
▪ Leukotriene antagonist	108 (2.6)	731 (1.7)	0.000
▪ Methylxanthine	80 (1.9)	564 (1.3)	0.004
▪ Mean no. of SABA prescriptions (SD)	1.3 (1.3)	1.0 (1.1)	0.000*
▪ Oral steroid	-	-	
Comorbidity			
▪ Nasal polyps	200 (4.7)	1570 (3.7)	0.002
▪ Mean BMI (SD)	30.2 (6.3)	29.7 (6.0)	0.000*
▪ Mean Charlson co-morbidity score (SD)	1.8 (1.4)	2.0 (1.5)	0.000*
Smoking status			
▪ Current smoker	444 (10.5)	4132 (9.9)	0.198
▪ Ex-smoker	1885 (44.5)	18047 (43.1)	0.074
▪ Non-smoker	1779 (42.0)	18209 (43.5)	0.068
▪ Missing	126 (3.0)	1493 (3.6)	
Previous hospitalisation for asthma	115 (2.7)	602 (1.4)	0.000
RTI recorded in the 90 days prior to index date	597 (14.1)	2001 (4.8)	0.000
Hospitalisation in the 90 days prior to index date	311 (7.3)	3200 (7.6)	0.490
Asthma review in the 365 days prior to index date	2104 (49.7)	18905 (45.1)	0.000

*Continuous variable analysed using ANOVA, otherwise variables are categorical analysed using the Chi-square test.

SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection, BMI = Body mass index. Cases and controls matched on age category, gender, calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

Oral non-selective beta-blocker exposure

The most commonly prescribed non-selective beta-blockers were sotalol and carvedilol.

The crude and adjusted associations between oral non-selective beta-blocker exposure and asthma events are shown in table 34. Due to low power for the 30 day risk windows, it was only possible to estimate the relative incidence for asthma death using the 60 and 90 day risk window for total and prevalent exposure. The relative incidence of asthma death was not significantly increased with non-selective beta-blocker exposure using the 60 and 90 day risk window (IRR 9.30 (95% CI 0.43 to 202.56) and IRR 10.52 (95% CI 0.46-243.09) respectively). It was not possible to estimate relative incidence for incident non-selective beta-blocker exposure. There was no significant difference found for prevalent non-selective beta-blocker exposure in the 60 and 90 day risk window. All exposure was prevalent exposure and a large but non-significant increase in the relative incidence of asthma death was observed.

Overall, there was no significant increase in the relative incidence of asthma hospitalisation associated with any non-selective beta-blocker exposure (incident and prevalent combined) with any of the risk windows (table 34). When stratified by type of exposure, exposure consisted of prevalent exposure only and no significant increase was observed.

Table 34. Crude and adjusted incidence rate ratios for the association between oral non-selective beta-blocker exposure and asthma events.

Risk window	Any				Incident				Prevalent			
	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value
Death												
▪ 30 day	-	-	-	-	-	-	-	-	-	-	-	-
▪ 60 day	5.00	9.30	0.43-202.56	0.156	-	-	-	-	5.00	9.30	0.43-202.56	0.156
▪ 90 day	5.00	10.52	0.46-243.09	0.142	-	-	-	-	5.00	10.81	0.46-253.28	0.139
Hospitalisation												
▪ 30 day	0.52	0.57	0.06-5.41	0.627	-	-	-	-	0.52	0.57	0.06-5.41	0.627
▪ 60 day	1.00	1.33	0.32-5.50	0.698	-	-	-	-	1.07	1.38	0.33-5.79	0.658
▪ 90 day	0.83	1.06	0.27-4.20	0.934	-	-	-	-	0.88	1.09	0.27-4.37	0.901
PACAE												
▪ 30 day	1.34	1.39	0.89-2.18	0.146	2.79	3.35	0.89-12.58	0.073	1.25	1.28	0.79-2.05	0.316
▪ 60 day	1.33	1.40	0.95-2.08	0.090	5.19	5.21	1.83-14.90	0.002	1.13	1.20	0.78-1.84	0.419
▪ 90 day	1.25	1.29	0.88-1.90	0.192	3.83	3.91	1.44-10.63	0.007	1.07	1.12	0.74-1.71	0.596

*Adjustment for confounders listed in table 30 (page 219). Empty cells = inestimable due to lack of exposure in the risk window.

Overall, there was no significant increase in the relative incidence of PCAE associated with any non-selective beta-blocker exposure (incident and prevalent combined) with any of the risk windows. When stratified by type of exposure, an increase in the relative incidence of PCAE was observed with incident non-selective exposure which was significant for the 60 and 90 day risk window (IRR 3.35 (95% CI 0.89 to 12.58), IRR 5.21 (95% CI 1.83 to 14.90) and IRR 3.91 (95% CI 1.44 to 10.63) for the 30, 60 and 90 day risk windows respectively). No significant increase in the relative incidence of PCAE was observed with prevalent non-selective beta-blocker exposure.

The association between oral non-selective beta-blocker exposure and asthma hospitalisation and PCAE according to dose are shown in table 35. Overall, there was a significant increase in the relative incidence of asthma hospitalisation with high dose non-selective beta-blocker exposure which was significant for the 60 and 90 day risk windows (IRR 15.79 (95% CI 1.30 to 191.77) and 11.17 (95% CI 1.07 to 116.26) respectively). It was not possible to obtain an estimate for the 30 day risk window due to an absence of high dose oral non-selective beta-blocker exposure among the cases and controls. When stratified by type of exposure, only prevalent high dose non-selective beta-blocker exposure was present which produced similar significant increases in relative incidence of asthma hospitalisation compared to any exposure.

Table 35. Incidence rate ratios for the association between oral non-selective beta-blocker exposure and asthma events by dose.

Risk window	Any				Incident				Prevalent			
	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value
High dose												
Hospitalisation												
▪ 30 day	-	-	-	-	-	-	-	-	-	-	-	-
▪ 60 day	5.00	15.79	1.30-191.77	0.030	-	-	-	-	5.00	15.49	1.27-189.36	0.032
▪ 90 day	3.33	11.17	1.07-116.26	0.044	-	-	-	-	3.33	11.03	1.06-115.18	0.045
PCAE												
▪ 30 day	2.50	2.70	1.00-7.29	0.049	-	-	-	-	2.50	2.71	1.00-7.30	0.049
▪ 60 day	2.50	2.69	1.08-6.67	0.033	-	-	-	-	2.50	2.68	1.08-6.65	0.034
▪ 90 day	2.92	3.17	1.35-7.45	0.008	10.00	9.72	0.57-165.97	0.116	2.61	2.73	1.09-6.83	0.032
Low to moderate dose												
Hospitalisation												
▪ 30 day	0.55	0.59	0.06-5.56	0.642	-	-	-	-	0.55	0.59	0.06-5.61	0.645
▪ 60 day	0.71	0.76	0.14-4.13	0.752	-	-	-	-	0.77	0.79	0.14-4.34	0.783
▪ 90 day	0.61	0.63	0.12-3.25	0.580	-	-	-	-	0.64	0.64	0.12-3.36	0.601
PCAE												
▪ 30 day	1.19	1.22	0.74-2.02	0.432	2.79	3.36	0.89-12.58	0.073	1.07	1.08	0.63-1.86	0.783
▪ 60 day	1.18	1.24	0.80-1.90	0.337	5.19	5.21	1.82-14.92	0.002	0.94	0.99	0.60-1.62	0.960
▪ 90 day	1.10	1.13	0.74-1.73	0.574	3.60	3.54	1.31-9.51	0.012	0.90	0.89	0.54-1.46	0.642

*Adjustment for confounders listed in table 30 (page 219). Empty cells = inestimable due to lack of exposure in the risk window.

Overall, there was a significant increase in the relative incidence of PCAE with high dose non-selective beta-blocker exposure for all risk windows (IRR 2.70 (95% CI 1.00 to 7.29), IRR 2.69 (95% CI 1.08 to 6.67) and IRR 3.17 (95% CI 1.35 to 7.45) for the 30, 60 and 90 day risk windows respectively). When stratified by type of exposure, prevalent high dose non-selective beta-blocker exposure produced similar significant increases in relative incidence of PCAE compared to any exposure. It was possible to calculate relative incidence of PCAE for incident high dose exposure using a 90 day risk window only and was non-significant (IRR 9.72 (95% CI 0.57 to 165.97)).

Overall, there was no significant increase in the relative incidence of PCAE with any low to moderate dose non-selective beta-blocker exposure for any of the risk windows evaluated. When stratified by type of exposure, an increase in the relative incidence of PCAE was observed with incident non-selective exposure which was significant for the 60 and 90 day risk window (IRR 3.35 (95% CI 0.89 to 12.58), IRR 5.21 (95% CI 1.82 to 14.92) and IRR 3.54 (95% CI 1.31 to 9.51) for the 30, 60 and 90 day risk windows respectively). No significant increase in the relative incidence of PCAE was observed with prevalent low to moderate dose non-selective beta-blocker exposure.

Oral selective beta-blocker exposure

The most commonly prescribed selective beta-blockers were atenolol and bisoprolol. The crude and adjusted associations between oral selective beta-blocker exposure and asthma events are shown in table 36. It was only possible to estimate the relative incidence for asthma death using the 90 day risk window which was not significantly different. This exposure consisted of prevalent exposure only and therefore it was not possible to estimate relative incidence for incident selective beta-blocker exposure.

Table 36. Crude and adjusted rate ratios for the association between oral selective beta-blocker exposure and asthma events.

Risk window	Any				Incident				Prevalent			
	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value
Death												
▪ 30 day	-	-	-	-	-	-	-	-	-	-	-	-
▪ 60 day	-	-	-	-	-	-	-	-	-	-	-	-
▪ 90 day	0.42	1.43	0.16-12.72	0.746	-	-	-	-	0.50	1.72	0.19-15.94	0.635
Hospitalisation												
▪ 30 day	0.84	1.08	0.66-1.79	0.753	0.98	0.88	0.07-10.89	0.920	0.83	1.09	0.66-1.82	0.731
▪ 60 day	0.76	0.99	0.62-1.56	0.948	2.07	1.71	0.47-6.26	0.419	0.67	0.92	0.56-1.51	0.747
▪ 90 day	0.83	1.01	0.66-1.54	0.980	1.70	2.00	0.65-6.13	0.225	0.74	0.92	0.58-1.45	0.721
PCAE												
▪ 30 day	0.81	0.87	0.75-1.01	0.061	1.03	1.00	0.50-2.04	0.989	0.81	0.86	0.74-1.00	0.056
▪ 60 day	0.89	0.96	0.85-1.09	0.563	0.85	0.86	0.50-1.47	0.578	0.89	0.97	0.85-1.10	0.622
▪ 90 day	0.89	0.98	0.87-1.10	0.698	0.66	0.69	0.43-1.11	0.130	0.91	1.00	0.88-1.13	0.996

*Adjustment for confounders listed in table 30 (page 219). Empty cells = inestimable due to lack of exposure in the risk window.

Overall, there was no statistically significant increase in the relative incidence of asthma hospitalisation associated with any oral selective beta-blocker exposure (incident and prevalent combined) with any of the risk windows overall (table 36). There was no statistically significant increase in the relative incidence of asthma hospitalisation associated with prevalent selective beta-blocker exposure.

Overall, there was no statistically significant increase in the relative incidence of PCAE associated with any oral selective beta-blocker exposure (incident and prevalent combined) with any of the risk windows overall (table 36). When stratified by type of exposure, there was no statistically significant increase in the relative incidence of asthma hospitalisation associated with incident or prevalent oral selective beta-blocker exposure.

The association between oral non-selective beta-blocker exposure and asthma hospitalisation and PCAE according to dose are shown in table 37. There was no statistically significant increase in the relative incidence of asthma hospitalisation with any dose of selective beta-blocker exposure. When stratified by type of exposure, there was no statistically significant increase in the relative incidence of asthma hospitalisation associated with high dose incident selective beta-blocker exposure although effect estimates were generally larger. It was not possible to calculate the relative incidence for incident exposure using a 30 day risk window due to a lack of power. There was no statistically significant increase in the relative incidence of asthma hospitalisation associated with any dose of prevalent selective beta-blocker exposure.

Table 37. Incidence rate ratios for the association between oral selective beta-blocker exposure and asthma events by dose.

Risk window	Any				Incident				Prevalent			
	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value
High dose												
Hospitalisation												
▪ 30 day	1.11	1.54	0.51-4.63	0.443	-	-	-	-	1.18	1.61	0.53-4.87	0.403
▪ 60 day	0.89	1.31	0.44-3.88	0.633	2.00	3.77	0.42-34.24	0.238	0.75	1.01	0.29-3.52	0.984
▪ 90 day	0.89	1.13	0.43-3.01	0.804	1.43	2.43	0.28-21.22	0.422	0.82	0.95	0.32-2.80	0.926
PCAE												
▪ 30 day	0.89	0.96	0.69-1.34	0.792	0.90	1.03	0.24-4.50	0.964	0.89	0.94	0.67-1.33	0.744
▪ 60 day	0.99	1.09	0.82-1.43	0.561	0.49	0.52	0.12-2.18	0.369	1.03	1.13	0.85-1.49	0.403
▪ 90 day	1.01	1.10	0.85-1.43	0.477	0.52	0.57	0.18-1.83	0.344	1.06	1.16	0.88-1.51	0.293
Low to moderate dose												
Hospitalisation												
▪ 30 day	0.79	1.00	0.57-1.73	0.985	0.89	0.79	0.07-9.21	0.849	0.79	1.01	0.57-1.79	0.969
▪ 60 day	0.74	0.98	0.60-1.60	0.943	1.52	1.56	0.43-5.63	0.498	0.67	0.91	0.54-1.55	0.736
▪ 90 day	0.80	1.01	0.64-1.59	0.965	1.34	1.81	0.59-5.57	0.301	0.73	0.91	0.55-1.51	0.721
PCAE												
▪ 30 day	0.81	0.86	0.73-1.01	0.063	1.33	1.25	0.67-2.34	0.489	0.78	0.83	0.70-0.99	0.039
▪ 60 day	0.87	0.95	0.82-1.09	0.419	1.02	0.98	0.60-1.60	0.926	0.86	0.95	0.82-1.09	0.448
▪ 90 day	0.88	0.96	0.84-1.09	0.529	0.81	0.82	0.54-1.27	0.378	0.89	0.98	0.85-1.12	0.757

*Adjustment for confounders listed in table 30 (page 219). Empty cells = inestimable due to lack of exposure in the risk window.

There was no statistically significant increase in the relative incidence of PCAE with any dose of selective beta-blocker exposure. When stratified by type of exposure, there was no statistically significant increase in the relative incidence of PCAE associated with incident or prevalent selective beta-blocker exposure with any dose.

Nested case control sensitivity analyses

Results from sensitivity analyses are presented in tables 38 and 39 for oral non-selective and selective beta-blocker exposure respectively.

1. Excluding patients hospitalised within the risk period

This was done to assess any impact of immortal time bias. For asthma hospitalisation, this involved excluding 43 (7.4%), 63 (10.8%) and 80 (13.7%) cases for the 30, 60 and 90 day risk windows respectively whilst for PCAE this involved excluding 111 (2.6%), 201 (4.8%) and 311 (7.4%) cases for the 30, 60 and 90 day risk windows respectively. This analysis produced similar results to the main analysis (shown in tables 38 and 39). For oral non-selective beta-blockers, effect estimates were slightly larger for both asthma hospitalisation and PCAE although the number of estimates which were significant remained unchanged.

2. Excluding patients diagnosed with asthma over the age of 45 years

This was done to assess any impact of including patients who may have unknown fixed airway obstruction. For asthma hospitalisation, this involved excluding 388 (66.3%) of cases whilst for PCAE this involved excluding 3103 (73.3%) of cases. For non-selective beta-blockers, this analysis produced effect estimates which were larger than the main analysis although all were non-significant due to a reduction in power

Table 38. Non-selective cardiovascular beta-blocker sensitivity analyses as per methods.

	IRR	Any 95% CI	IRR	Incident 95% CI	IRR	Prevalent 95% CI
Hospitalised in risk window						
Hospitalisation						
30 day	0.63	0.06-6.35	-	-	0.63	0.06-6.36
60 day	1.51	0.34-6.33	-	-	1.51	0.34-6.34
90 day	1.63	0.37-7.13	-	-	1.63	0.37-7.14
PCAE						
30 day	1.46	0.93-2.26	3.64	0.95-13.92	1.32	0.82-2.13
60 day	1.44	0.96-2.16	6.19	1.61-23.83	1.29	0.84-1.99
90 day	1.41	0.94-2.10	4.24	1.18-15.16	1.28	0.84-1.97
Diagnosed with asthma ≥ 45						
Hospitalisation						
30 day	-	-	-	-	-	-
60 day	3.06	0.35-26.67	-	-	3.06	0.35-26.67
90 day	1.81	0.20-16.20	-	-	1.81	0.20-16.19
PCAE						
30 day	1.09	0.33-3.61	7.75	0.42-142.11	0.77	0.18-3.28
60 day	1.50	0.58-3.87	7.70	0.42-140.92	1.26	0.44-3.60
90 day	1.26	0.49-3.24	2.64	0.25-28.02	1.12	0.40-3.19
Smokers over 40 years						
Hospitalisation						
30 day	0.53	0.06-5.08	-	-	0.53	0.06-5.08
60 day	1.28	0.31-5.35	-	-	1.33	0.31-5.63
90 day	1.06	0.26-4.27	-	-	1.08	0.26-4.45
PCAE						
30 day	1.52	0.96-2.39	5.06	1.23-20.79	1.36	0.84-2.21
60 day	1.45	0.97-2.17	7.37	2.35-23.12	1.21	0.77-1.89
90 day	1.34	0.90-1.99	4.85	1.69-13.89	1.14	0.74-1.76
Unmatched on age						
Hospitalisation						
30 day	0.56	0.06-5.33	-	-	0.56	0.06-5.33
60 day	1.32	0.32-5.47	-	-	1.37	0.33-5.77
90 day	1.06	0.27-4.20	-	-	1.09	0.27-4.37
PCAE						
30 day	1.34	0.85-2.10	3.35	0.89-12.57	1.22	0.75-1.98
60 day	1.36	0.91-2.02	5.22	1.83-14.90	1.15	0.74-1.78
90 day	1.25	0.85-1.85	3.92	1.44-10.63	1.08	0.70-1.66
Complete case analysis						
Hospitalisation						
30 day	0.62	0.06-6.10	-	-	0.62	0.06-6.11
60 day	1.49	0.35-6.39	-	-	1.56	0.36-6.83
90 day	1.14	0.28-4.63	-	-	1.18	0.29-4.84
PCAE						
30 day	1.43	0.91-2.27	3.13	0.83-11.75	1.32	0.81-2.15
60 day	1.47	0.98-2.19	4.96	1.74-14.14	1.25	0.80-1.94
90 day	1.37	0.92-2.02	3.74	1.38-10.14	1.19	0.77-1.83

Sensitivity analyses excluding patients: hospitalised within the risk window; smokers >40 years of age; diagnosed with asthma >45 years of age; unmatched on age; complete case analysis.

Table 39. Selective cardiovascular beta-blocker sensitivity analyses as per methods.

	Any		Incident		Prevalent	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Hospitalised in risk window						
Hospitalisation						
30 day	1.13	0.67-1.91	-	-	1.15	0.68-1.95
60 day	1.02	0.62-1.68	1.89	0.44-8.25	0.95	0.56-1.63
90 day	0.92	0.56-1.53	0.41	0.04-3.79	0.97	0.58-1.63
PCAE						
30 day	0.86	0.74-1.01	0.93	0.42-2.05	0.86	0.74-1.01
60 day	0.96	0.84-1.09	0.78	0.41-1.50	0.96	0.84-1.10
90 day	0.97	0.85-1.10	0.55	0.29-1.04	1.00	0.87-1.14
Diagnosed with asthma ≥45						
Hospitalisation						
30 day	0.53	0.15-1.85	1.58	0.07-36.27	0.44	0.10-1.87
60 day	0.62	0.21-1.83	0.64	0.05-8.23	0.62	0.19-2.04
90 day	0.86	0.35-2.10	0.63	0.06-6.46	0.91	0.35-2.37
PCAE						
30 day	0.72	0.50-1.04	0.59	0.14-2.57	0.73	0.50-1.07
60 day	0.85	0.63-1.15	0.79	0.31-2.02	0.86	0.63-1.18
90 day	0.88	0.66-1.16	0.62	0.27-1.43	0.92	0.68-1.24
Smokers over 40 years						
Hospitalisation						
30 day	1.00	0.58-1.73	1.03	0.06-17.41	1.00	0.57-1.75
60 day	0.88	0.53-1.46	2.23	0.56-8.81	0.73	0.41-1.28
90 day	0.89	0.56-1.42	2.47	0.78-7.89	0.72	0.43-1.22
PCAE						
30 day	0.89	0.76-1.04	1.14	0.56-2.34	0.88	0.75-1.03
60 day	0.99	0.87-1.14	0.93	0.54-1.61	1.00	0.87-1.14
90 day	1.00	0.88-1.14	0.78	0.48-1.26	1.02	0.89-1.17
Unmatched on age						
Hospitalisation						
30 day	1.09	0.66-1.80	0.89	0.07-11.12	1.10	0.66-1.84
60 day	0.99	0.63-1.57	1.72	0.47-6.32	0.93	0.57-1.52
90 day	1.01	0.66-1.55	2.02	0.66-6.19	0.92	0.58-1.46
PCAE						
30 day	0.87	0.75-1.01	1.01	0.50-2.04	0.86	0.74-1.01
60 day	0.97	0.85-1.10	0.86	0.50-1.47	0.97	0.85-1.10
90 day	0.98	0.87-1.11	0.70	0.43-1.12	1.00	0.88-1.14
Complete case analysis						
Hospitalisation						
30 day	1.09	0.66-1.82	0.88	0.08-10.49	1.11	0.66-1.86
60 day	1.00	0.63-1.59	1.65	0.43-6.31	0.94	0.57-1.55
90 day	1.02	0.66-1.57	2.03	0.64-6.47	0.93	0.59-1.48
PCAE						
30 day	0.87	0.74-1.01	1.00	0.49-2.03	0.86	0.74-1.01
60 day	0.96	0.84-1.09	0.90	0.52-1.55	0.96	0.84-1.10
90 day	0.98	0.86-1.11	0.74	0.46-1.18	1.00	0.88-1.13

Sensitivity analyses excluding patients: hospitalised within the risk window; smokers >40 years of age; diagnosed with asthma >45 years of age; unmatched on age; complete case analysis.

3. Excluding patients over the age of 40 years who smoked

This was done to again assess any impact of including patients who may have unknown fixed airway obstruction. For asthma hospitalisation, this involved excluding 46 (7.9%) of cases whilst for PCAE this involved excluding 395 (9.3%) of cases. For the association between non-selective beta-blockers and PCAE, effect estimates were larger than the main analysis with incident exposure being significant for all three risk windows (IRR 5.06 (95% CI 1.23 to 20.79), 7.37 (95% CI 2.35 to 23.12) and 4.85 (95% CI 1.69 to 13.89) for the 30, 60 and 90 day risk windows respectively). For selective beta-blockers, effect estimates for asthma hospitalisation and PCAE were slightly larger than the main analysis although no changes in overall significance were observed.

4. Excluding patients originally unmatched on age

This was done to assess for any residual confounding by age. For asthma hospitalisation, this involved excluding 2 (0.3%) of cases whilst for PCAE this involved excluding 8 (0.2%) of cases. This analysis produced almost identical results the main analysis with no overall changes in significance.

5. Complete case analysis

This was done to assess the impact of multiply imputing missing data. For asthma hospitalisation, data was missing on height, weight and smoking status for 78 (1.2%), 71 (1.1%) and 186 (2.9%) of people respectively whilst for PCAE data was missing on height, weight and smoking status for 604 (1.3%), 526 (1.1%) and 1619 (3.5%) of people respectively. Results were very similar to the main analysis with a significantly increased risk of PCAE with incident oral non-selective beta-blocker exposure.

8.4.2 Secondary analyses using the self-controlled case series

The two SCCS analyses consisted of 27 patients (mean age 68.6 years, 48% women) with incident non-selective beta-blocker exposure experiencing a total of 36 PCAEs, and 185 patients (mean age 64.0 years, 49% women) with incident selective beta-blocker exposure experiencing 239 PCAEs during the study period. Non-selective beta-blockers consisted of carvedilol and sotalol whilst the most common selective beta-blockers were bisoprolol and atenolol. The number of events, total person time and crude incidence of PCAE for the baseline period, pre-risk period, acute risk period and the chronic risk period is shown in table 40. As expected, the crude incidence of PCAE was lower during the pre-risk period for both non-selective and selective beta-blocker exposure.

For non-selective and selective beta-blockers, the crude incidence of PCAE was greater during the acute risk period compared to baseline for each analysis (table 40). The crude and adjusted relative incidence of PCAE associated with oral beta-blocker exposure is shown in table 41. For both analyses only low to moderate dose exposure could be evaluated. Overall, the relative incidence of PCAE increased among all acute risk periods with non-selective beta-blocker exposure, which was statistically significant using the 30 day risk period only and became smaller with increasing risk period duration (IRR 3.14 (95% CI 1.28 to 7.74), IRR 1.82 (95% CI 0.78 to 4.23) and IRR 1.32 (95% CI 0.59 to 2.96) for the 30, 60 and 90 day acute risk periods respectively). No significant increase was observed with chronic non-selective beta-blocker exposure. In contrast, there was no significant increase in the relative incidence of PCAE with selective beta-blocker exposure using any duration of risk period.

Table 40. Number of events, person time and crude incidence rates according to exposure group and risk window used in the cardiovascular beta-blocker self-controlled case series.

Risk period	Non-selective beta-blocker			Selective beta-blocker		
	Events	Person Time*	Crude Incidence [‡]	Events	Person Time*	Crude Incidence [‡]
30 day						
▪ Pre-risk	2	782	25.58	14	5254	26.65
▪ Baseline	22	6139	35.84	150	37477	40.02
▪ Acute	8	806	99.26	20	5583	35.82
▪ Chronic	4	1847	21.66	55	18380	29.92
60 day						
▪ Pre-risk	2	782	25.58	14	5254	26.65
▪ Baseline	22	5834	37.71	147	36277	40.52
▪ Acute	10	1615	61.92	36	11196	32.15
▪ Chronic	2	1343	14.89	42	13964	30.08
90 day						
▪ Pre-risk	2	782	25.58	14	5254	26.65
▪ Baseline	22	5447	40.39	139	34432	40.37
▪ Acute	12	2397	50.06	51	16800	30.36
▪ Chronic	0	934	-	34	10185	34.36

*Person time (days). [‡]Per 10,000 person years.

Table 41. Adjusted incidence rate ratios for oral non-selective and selective beta-blocker exposure and primary care asthma exacerbations used in the self-controlled case series.

Risk period	Non-selective beta-blocker			Selective beta-blocker		
	IRR	95% CI	p-value	IRR	95% CI	p-value
30 day						
▪ Baseline	1.00			1.00		
▪ Acute	3.14	1.28-7.74	0.013	0.87	0.51-1.48	0.600
▪ Chronic	0.69	0.20-2.37	0.553	0.74	0.49-1.11	0.147
60 day						
▪ Baseline	1.00			1.00		
▪ Acute	1.82	0.78-4.23	0.165	0.77	0.50-1.19	0.241
▪ Chronic	0.44	0.09-2.16	0.309	0.80	0.51-1.24	0.314
90 day						
▪ Baseline	1.00			1.00		
▪ Acute	1.32	0.59-2.96	0.501	0.71	0.48-1.06	0.093
▪ Chronic	-	-	-	0.97	0.60-1.58	0.907

*Adjusted for use of SABA, LABA, ICS, leukotriene receptor antagonists, methylxanthines and seasonal variation.

8.5 Discussion

This study investigated the association between oral beta-blockers commonly used for the management of CVD and asthma death, hospitalisation and PCAE. The primary analysis was the nested case control study which found an 11- to 15-fold increased risk of asthma hospitalisation associated with prevalent high dose non-selective beta-blocker exposure using a 60 and 90 day risk window. In contrast, no significant increase in asthma hospitalisation was seen with prevalent low dose non-selective beta-blocker exposure. In the nested case control study, a significant 3.5- to 5-fold increased risk of PCAE occurred with incident low to moderate dose non-selective beta-blocker exposure and a 2.7-fold increased risk of PCAE occurred with prevalent high dose non-selective beta-blocker exposure. In contrast, no significant increase in PCAE was seen with prevalent low to moderate dose non-selective beta-blocker exposure. These findings could be interpreted as a dose-response relationship for non-selective beta-blockers. The secondary analysis was the SCCS which found a significant 3-fold increased relative incidence of PCAE within 30 days of the first non-selective beta-blocker prescription only with risk falling with increasing risk period duration.

In the nested case control study, no significant increase in asthma hospitalisation or PCAE was associated with oral selective beta-blocker exposure although effect estimates were generally larger for incident high dose exposure and the association with asthma hospitalisation. No significant increase in the relative incidence of PCAE was seen in the secondary analysis using the SCCS. These findings suggest that selective beta-blockers prescribed to people with asthma in primary care did not lead to significantly increased numbers of serious asthma exacerbations.

Strengths and limitations

It was not possible to properly evaluate the risk of asthma death due to a lack of power. It was also not possible to properly evaluate the risk of asthma hospitalisation and of PCAE associated with incident non-selective beta-blocker exposure using the nested case control study due to a lack of power. This analysis was limited by the fact that high non-selective beta-blocker doses were not commonly prescribed to people in the asthma CVD cohort. In this analysis, non-selective beta-blockers consisted mainly of sotalol and carvedilol which have a 12-fold and 4.5-fold greater affinity for the beta₂- versus beta₁-adrenoceptor respectively (72). Although selective beta-blockers were not associated with an increased risk of asthma events in this analysis, a dose response relationship in respect to mean falls in FEV₁ was demonstrated for selective beta-blockers in the meta-analysis reported in chapter 3. Chapter 6 described the prevalence of beta-blocker prescribing in the CPRD active asthma cohort and showed that beta-blockers were prescribed at an average dose of 112mg for sotalol, 21mg for carvedilol, 47mg for atenolol and 4mg for bisoprolol. It was not possible to investigate the effect of high dose exposure using the SCCS because of a lack of patients with this exposure.

Effect estimates often had wide confidence intervals demonstrating a lack of precision in the size of the effect estimates. The large number of calculations performed may increase the likelihood of spuriously statistically significant findings as a result of repeat testing. On average, patients in the asthma CVD cohort were older than in the CPRD active asthma cohort which could raise concerns about the validity of results. This is because some patients may have a degree of fixed air-flow obstruction potentially underestimating the relative incidence of asthma events because selective beta-blockers are considered to be better tolerated as demonstrated by a meta-analysis of randomised

blinded placebo controlled trials in people with COPD where no significant fall in FEV1 occurred following selective beta-blocker exposure (87).

Two sensitivity analyses were chosen to test this assumption by first excluding patients over the age of 40 who smoked and second excluding people diagnosed with asthma over the age of 45 creating a population in which COPD is much less likely to occur unless a rare genetic condition such as alpha-1 anti-trypsin deficiency is present. For incident non-selective beta-blocker exposure, these sensitivity analyses produced slightly larger effect estimates than the main analysis suggesting some misclassification bias may be present. In contrast, these sensitivity analyses did not significantly change the results for selective beta-blockers. It is also uncertain from this analysis whether careful beta-blocker dose titration occurred in this population which may have minimized risk from non-selective beta-blockers.

The increased risk of PCAE using the SCCS presented in this chapter was observed using only a small sample size. However, the SCCS was originally designed to be used with small sample sizes to investigate rare adverse events associated with vaccine exposure (126). An increased risk of PCAE occurred within 30 days of incident non-selective beta-blocker prescribing in the SCCS with the effect estimates falling when the duration of the acute risk period increased. In contrast, a significantly increased risk of PCAE was detected in the nested case control study during the 60 and 90 day risk windows respectively. These differences in statistically significant effect estimates may be related to differences in study design and residual confounding or selection bias in the nested case control study. Despite these potential limitations, both study designs detected a significant increased risk from incident non-selective beta-blocker exposure.

For the nested case control study, the cohort of people with asthma and CVD was chosen to better ensure controls were sampled from a representative population. As previously discussed, beta-blockers may have been prescribed to people with less severe asthma and risk may be greater in people with more severe asthma. It remains unknown whether patients had this medication dispensed, when patients actually started taking their medication for the first time and how compliant people were with their medication regimes.

8.6 Summary

This chapter demonstrated an increased risk of adverse respiratory events associated with prevalent high dose and incident low to moderate dose non-selective beta-blocker exposure. In contrast, no significant increased risk of serious asthma exacerbations was observed with oral selective beta-blockers. This study suggests that people with asthma and CVD should be prescribed a selective rather than a non-selective beta-blocker and that people currently established on selective beta-blocker therapy for the management of CVD should not have their medication discontinued unless asthma symptoms are thought to be attributed to beta-blocker exposure. This study also suggests that selective beta-blockers should be more widely considered in people with asthma when clinically indicated and no alternatives exist. However, insufficient power meant it was not possible to properly evaluate the risk of asthma death. The different but complementary analytical approaches used provide some validity in the results although this is restricted to PCAE only. The following chapter will evaluate NSAID exposure using a similar approach whilst the discussion section in chapter 10 will provide further detail and a comparison of these results with other chapters.

Chapter 9: Adverse Respiratory Effect of NSAIDs in Asthma: Nested Case Control and Self-Controlled Case Series in People with Asthma Issued Low Strength Analgesics

9.1 Introduction

This chapter will evaluate the association between different types of NSAID prescribing and asthma mortality and morbidity. Aspirin and other NSAIDs trigger exacerbations in susceptible people with asthma. Chapter 4 estimated the prevalence of aspirin-exacerbated respiratory disease (AERD) from studies performing oral provocation challenge tests and population studies measuring self-reported history of AERD. The findings were that around 9% of people with asthma have AERD which is triggered at clinically relevant doses of aspirin. Chapter 5 measured the adverse respiratory effect from clinical trials evaluating acute selective NSAID and COX-2 inhibitors exposure in people with AERD, and showed that in this population COX-2 inhibitors did not trigger any adverse respiratory effects whilst selective NSAIDs triggered symptoms in approximately 8% of people with AERD. Although appropriately conducted clinical trials of COX-2 inhibitors in AERD have strong internal validity, real world assessment of the effect of NSAID exposure in the general asthma population is lacking. The drug utilisation study presented in chapter 6 also highlighted that NSAID prescribing among people with asthma is relatively common although COX-2 inhibitors are rarely prescribed despite their apparent better tolerability.

9.2 Aim

The aim of this chapter was to assess the adverse respiratory effect of oral NSAIDs and COX-2 inhibitors using linked electronic health data.

9.3 Methodology

Primary analysis using the nested case control study

Population

The nested case control study measured the association between oral NSAID exposure and asthma events in a cohort of people with asthma prescribed analgesic medications derived from the CPRD adult active asthma cohort (described in chapter 2, page 66).

Entry into the asthma analgesic cohort occurred on or after the date of entry to the CPRD active asthma cohort. The asthma analgesic cohort consisted of people in the CPRD active asthma cohort who were prescribed one or more low strength analgesic prescriptions during cohort follow-up defined as prescriptions for oral NSAIDs, oral paracetamol and compound preparations containing paracetamol and low strength opiates (co-codamol and co-dydramol prescriptions). Low strength analgesic prescriptions were chosen so that comparisons were made between people requiring similar levels of pain control in the absence of specific clinical indications. Therefore, the asthma analgesic cohort contains people with asthma and actively managed low level painful conditions.

Entry into the asthma analgesic cohort was defined as the date of the first low strength analgesic prescription prescribed on or after entry into the CPRD active asthma cohort. Cohort follow-up remained unchanged as previously described (chapter 2, page 67) but the asthma analgesic cohort was additionally censored at the end of exposure to low strength analgesic medication (defined below). In circumstances when exposure to low strength analgesic medication ceased before the end of follow-up, end of exposure was determined as the date of the last analgesic prescription with the addition of a 180 day

grace period. Analysis was restricted to people from practices which were linked to the HES and ONS databases providing full outcome ascertainment.

Case and control selection

Outcomes consisted of asthma death, asthma hospitalisation and PCAE as previously defined (chapter 2, pages 67). For each outcome, up to 10 controls were randomly selected and matched to each case on age (categorised into deciles), gender, calendar year of cohort entry and whether patients were diagnosed with asthma before the age of 45 using incidence density sampling. When a case could not be matched to one or more controls, the matching process was repeated without age. This was a pragmatic decision to include all cases and affected 3 cases (0.1%) of PCAE only.

Exposures

Oral NSAID exposure was defined as current incident user, current prevalent user and non-user as described in the general methods chapter (chapter2, page 72). Among current users, exposure to oral NSAIDs was evaluated by selectivity as defined in chapter 2 (page 72). The association with oral NSAID exposure was evaluated using three risk windows consisting of 30, 60 and 90 days.

Confounders and data analysis

Multiple imputation was used to impute missing data on height, weight and smoking status as previously described (chapter 2, page 74). For each analysis, adjustment was made for the confounders listed in table 42 according to clinical relevance and model fit as previously described (chapter 2, page 73).

Table 42. Confounders used for risk adjustment in the nested case control analysis between NSAIDs and asthma death, asthma hospitalisation and primary care asthma exacerbation.

Characteristic	Death	Hospitalisation	PCAE
Exact age [¥]	Yes	Yes	Yes
Deprivation [€]	Yes	Yes	Yes
Medications*			
▪ ICS	Yes	Yes	Yes
▪ LABA	Yes	Yes	Yes
▪ LABAICS	Yes	Yes	Yes
▪ Leukotriene antagonist	Yes	Yes	Yes
▪ Methylxanthine	Yes	Yes	Yes
▪ No. of SABA [¥]	Yes	Yes	Yes
▪ Oral steroid	Yes	Yes	No
▪ NSAIDs	Yes	Yes	Yes
Comorbidity			
▪ Nasal polyps	No	Yes	Yes
▪ BMI [¥]	Yes	Yes	Yes
▪ Charlson co-morbidity score [¥]	Yes	Yes	Yes
Smoking status	Yes	Yes	Yes
Previous asthma hospitalisation	Yes	Yes	Yes
RTI*	Yes	Yes	Yes
Asthma review ^δ	No	No	Yes

*= In the 90 days prior to index date. €= Index of multiple deprivation decile.

δ = In the 365 days prior to index date.

¥ = Continuous variable. PCAE = primary care asthma exacerbation.

Chi-squared testing and analysis of variance (ANOVA) was used to determine statistically significant differences in patient characteristics between cases and controls. Conditional logistic regression was used to estimate odds ratios which represent incidence rate ratios for the association between NSAID exposure and asthma events.

Nested case control sensitivity analyses

The following sensitivity analyses were performed to test the robustness of the results:

- excluding patients hospitalised within the risk period

- excluding patients over the age of 40 years who smoked
- excluding patients diagnosed with asthma over the age of 45
- excluding patients not originally matched on age (i.e. not matched on age, since this is the matching variable dropped in the second round)
- complete case analysis

Secondary analysis using the self-controlled case series

The SCCS method has previously defined in chapter 2 (page 77). The SCCS was conducted over a 360 day study period centred on incident oral NSAID exposure (first prescription in the file in people with at least 1 year of follow up prior to the first prescription) as previously defined (chapter 2 page 77). The beginning of the observation period was defined as 180 days prior to the date of the incident oral NSAID prescription and the end of the observation period was defined as 180 days following this incident prescription. The SCCS was performed for PCAE as previously defined, using 30 day, 60 day and 90 day acute risk periods beginning on the incident prescription date for oral NSAID. Exposure beyond these risk windows was categorised as chronic exposure. A 30 day pre-risk period was used to account for short-lived event dependent exposures. All remaining person time was classed as baseline.

Confounders and data analysis

Time-varying exposure to the following medications issued within 90 day consecutive periods was adjusted for in the analysis as previously described (chapter2, page 81): ICS; inhaled LABAs; leukotriene antagonists; methlyxanthines; and the total number of SABA prescriptions. Additional risk adjustment was made for seasonal variation. Crude

and adjusted incidence rate ratios (IRR) were calculated using conditional Poisson regression with analyses stratified by selectivity as previously defined (page 69).

9.4 Results

The asthma analgesic cohort consisted of 148443 patients with a mean age at cohort entry of 43.9 years (SD 16.5) and more women than men (64.2% vs. 35.8% respectively). During follow-up of the asthma analgesic cohort, a total of 27 asthma deaths, 583 asthma hospitalisations occurred and 5302 PCAE occurred. Non-selective NSAIDs were prescribed to 30281 (39.3%), NSAIDs with <5-fold COX-2 selectivity were prescribed to 37902 (49.2%), NSAIDs with 5- to 50-fold COX-2 selectivity were prescribed to 3026 (3.9%) and COX-2 inhibitors were prescribed to 5898 (7.6%) in the asthma analgesic cohort during mean follow-up of 2.2 years.

9.4.1 Primary analysis using the nested case control study

Asthma death

All cases of asthma death were matched to controls. Table 43 describes characteristics of the 27 cases of asthma death matched to 259 controls. There were no statistically significant differences in matching criteria between cases and controls. Cases died of asthma at a mean age of 64.9 years and were predominantly women (74.1%). Cases had a statistically significant higher use of LABA prescribed as a separate inhaler, SABAs and oral steroids within 90 days of the index date. A statistically greater proportion of cases had a previous asthma hospitalisation, were hospitalised for any cause and had a respiratory tract infection within 90 days of the index date. Cases had a statistically lower average BMI.

Table 43. Characteristics of cases and controls for asthma death in the NSAID analysis.

Characteristics	Cases N=27	Controls N=259	p-value
Matching variables			
Age (years, SD)	64.9 (14.9)	63.4 (13.5)	0.580*
Female gender	20 (74.1)	200 (77.2)	0.712
Years of follow-up to index date (years, SD)	2.5 (3.0)	2.3 (2.8)	0.714*
Diagnosed with asthma \leq age 45	10 (37.0)	98 (37.8)	0.935
Potential confounders			
Asthma therapy in the 90 days prior to index date			
▪ ICS	12 (44.4)	129 (49.8)	0.596
▪ LABA	7 (25.9)	29 (11.2)	0.028
▪ LABAICS	5 (18.5)	46 (17.8)	0.922
▪ Leukotriene antagonist	3 (11.1)	9 (3.5)	0.168
▪ Methylxanthine	3 (11.1)	10 (3.9)	0.217
▪ Mean no. of SABA prescriptions (SD)	2.4 (2.9)	1.3 (1.4)	0.001*
▪ Oral steroid	12 (44.4)	16 (6.2)	0.000
Comorbidity			
▪ Nasal polyps	0 (0.0)	7 (2.7)	0.833
▪ Mean BMI (SD)	26.3 (5.7)	29.4 (6.3)	0.022*
▪ Mean Charlson co-morbidity score (SD)	2.0 (1.0)	1.7 (1.2)	0.248*
Smoking status			
▪ Current smoker	5 (18.5)	38 (14.7)	0.595
▪ Ex-smoker	6 (22.2)	91 (35.1)	0.177
▪ Non-smoker	11 (40.7)	103 (39.8)	0.922
▪ Missing	5 (18.5)	27 (10.4)	
Previous hospitalisation for asthma	4 (14.8)	8 (3.1)	0.017
RTI recorded in the 90 days prior to index date	9 (33.3)	14 (5.4)	0.000
Hospitalisation in the 90 days prior to index date	13 (48.1)	27 (10.4)	0.000
Asthma review in the 365 days prior to index date	10 (37.0)	101 (39.0)	0.842

*Continuous variable analysed using ANOVA, otherwise variables are categorical analysed using the Chi-square test.

SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection,

BMI = Body mass index. Cases and controls matched on age category, gender, calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

Asthma hospitalisation

All cases of asthma hospitalisation were matched to controls. Table 44 describes the characteristics of the 583 cases of asthma hospitalisation matched to 5765 controls.

There were no statistically significant differences in matching criteria between cases and controls. Cases were hospitalised for asthma at a mean age of 47.5 years and were predominantly women (81.0%). Cases had a statistically significant higher use of all types of asthma medication. A greater proportion of cases had a respiratory tract infection recorded, had previously been hospitalised for asthma and had been hospitalised for any cause within 90 days of the index date which was statistically significant. Cases had clinically small but a statistically significant greater mean BMI.

Table 44. Characteristics of cases and controls for asthma hospitalisation in the NSAID analysis.

Characteristics	Cases N=583	Controls N=5765	p-value
Matching variables			
Age (years, SD)	47.5 (17.2)	47.5 (17.3)	0.964*
Female gender	472 (81.0)	4699 (81.5)	0.745
Years of follow-up to index date (years, SD)	1.4 (2.3)	1.3 (2.3)	0.668*
Diagnosed with asthma \leq age 45	376 (64.5)	3710 (64.4)	0.946
Potential confounders			
Asthma therapy in the 90 days prior to index date			
▪ ICS	299 (51.3)	2510 (43.5)	0.000
▪ LABA	126 (21.6)	476 (8.3)	0.000
▪ LABAICS	175 (30.0)	976 (16.9)	0.000
▪ Leukotriene antagonist	68 (11.7)	153 (2.7)	0.000
▪ Methylxanthine	67 (11.5)	123 (2.1)	0.000
▪ Mean no. of SABA prescriptions (SD)	2.3 (2.0)	1.2 (1.4)	0.000*
▪ Oral steroid	255 (43.7)	367 (6.4)	0.000
Comorbidity			
▪ Nasal polyps	14 (2.4)	121 (2.1)	0.629
▪ Mean BMI (SD)	30.9 (9.0)	29.6 (7.2)	0.000*
▪ Mean Charlson co-morbidity score (SD)	1.5 (1.3)	1.5 (1.1)	0.077*
Smoking status			
▪ Current smoker	150 (25.7)	1510 (26.2)	0.808
▪ Ex-smoker	173 (29.7)	1703 (29.5)	0.946
▪ Non-smoker	211 (36.2)	2205 (38.2)	0.330
▪ Missing	49 (8.4)	347 (6.0)	
Previous hospitalisation for asthma	143 (24.5)	192 (3.3)	0.000
RTI recorded in the 90 days prior to index date	127 (21.8)	518 (9.0)	0.000
Hospitalisation in the 90 days prior to index date	109 (18.7)	581 (10.1)	0.000
Asthma review in the 365 days prior to index date	225 (38.6)	2044 (35.5)	0.132

*Continuous variable analysed using ANOVA, otherwise variables are categorical analysed using the Chi-square test.

SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection, BMI = Body mass index. Cases and controls matched on age category, gender, calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

Primary care asthma exacerbations

Three cases (0.1%) were included unmatched on age. Table 45 describes the characteristics of the 5302 cases of PCAE matched to 52381 controls. There were no statistically significant differences in matching criteria between cases and controls. PCAEs occurred at a mean age of 50.3 years predominantly in women (73.0%). Cases had a statistically significant greater use of all asthma medications. A greater proportion of cases had attended an asthma review in the previous year, had a respiratory tract infection recorded within 90 days of the index date and had previously been hospitalised for asthma which was statistically significant. Cases had a small but statistically significant higher mean BMI and lower Charlson comorbidity score. Cases had a statistically significant greater proportion of people with nasal polyps and people who were current smokers.

Table 45. Characteristics of cases and controls for primary care asthma exacerbations in the NSAID analysis.

Characteristics	Cases N=5302	Controls N=52381	p-value
Matching variables			
Age (years, SD)	50.3 (16.9)	50.2 (16.9)	0.599*
Female gender	3868 (73.0)	38450 (73.4)	0.479
Years of follow-up to index date (years, SD)	0.8 (1.8)	0.8 (1.8)	0.453*
Diagnosed with asthma \leq age 45	2916 (55.0)	28700 (54.8)	0.806
Potential confounders			
Asthma therapy in the 90 days prior to index date			
▪ ICS	2565 (48.4)	21946 (41.9)	0.000
▪ LABA	557 (10.5)	3667 (7.0)	0.000
▪ LABAICS	1161 (21.9)	7725 (14.7)	0.000
▪ Leukotriene antagonist	197 (3.7)	1013 (1.9)	0.000
▪ Methylxanthine	117 (2.2)	783 (1.5)	0.000*
▪ Mean no. of SABA prescriptions (SD)	1.4 (1.5)	1.1 (1.2)	0.000
▪ Oral steroid	-	-	
Comorbidity			
▪ Nasal polyps	186 (3.5)	1168 (2.2)	0.000
▪ Mean BMI (SD)	29.6 (6.9)	29.2 (7.4)	0.000*
▪ Mean Charlson co-morbidity score (SD)	1.4 (1.0)	1.5 (1.1)	0.000*
Smoking status			
▪ Current smoker	1363 (25.7)	12094 (23.1)	0.000
▪ Ex-smoker	1701 (32.1)	16752 (32.0)	0.880
▪ Non-smoker	1960 (37.0)	20031 (38.2)	0.069
▪ Missing	278 (5.2)	3504 (6.7)	
Previous hospitalisation for asthma	370 (7.0)	1630 (3.1)	0.000
RTI recorded in the 90 days prior to index date	808 (15.2)	3937 (7.5)	0.000
Hospitalisation in the 90 days prior to index date	498 (9.4)	4967 (9.5)	0.832
Asthma review in the 365 days prior to index date	2142 (40.4)	18679 (35.7)	0.000

SD = standard deviation, ICS = inhaled corticosteroid, LABA = long-acting beta2-agonist, LABAICS = long-acting beta2-agonist in combination inhaler with ICS, SABA = short-acting beta2-agonist, RTI = respiratory tract infection, BMI = Body mass index. Cases and controls matched on age category, gender, calendar year of cohort entry and whether patients were diagnosed with asthma under the age of 45 years only.

Oral NSAID exposure

The most commonly prescribed NSAIDs according to selectivity were: ibuprofen for non-selective NSAIDs; diclofenac for NSAIDs with <5-fold COX-2 selectivity; meloxicam for NSAIDs with 5- to 50-fold COX-2 selectivity; and celecoxib for COX-2 inhibitors. The association between oral NSAID exposure and asthma events is shown in tables 46 to 49. It was not possible to estimate the relative incidence of asthma death for NSAIDs with 5- to 50-fold COX-2 selectivity due to a lack of NSAID exposure among the cases. Among the remaining classes of NSAID, the association with asthma death could only be determined for prevalent exposure. There was an increase in the relative incidence of asthma death with non-selective NSAIDs which was significant using the 90 day the risk window only (IRR 7.79 (95% CI 1.35 to 44.90), table 46). There was no significant increase in the relative incidence of asthma death with any other type of NSAID.

Overall, there was no significant increase in the relative incidence of asthma hospitalisation with any type of oral NSAID exposure (incident and prevalent combined, tables 46 to 49). When stratified by duration of administration (incident and prevalent), there was again no significant increase in the relative incidence of asthma hospitalisation with any class of oral NSAID. It was not possible to estimate the relative incidence of asthma hospitalisation with incident exposure to NSAIDs with ≥ 5 -fold COX-2 selectivity due to a lack of power.

Table 46. Crude and adjusted incidence rate ratios for the association between non-selective NSAID exposure and asthma events.

Risk window	Any				Incident				Prevalent			
	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value
Death												
▪ 30 day	1.31	3.31	0.38-29.19	0.280	-	-	-	-	1.66	5.79	0.65-50.16	0.115
▪ 60 day	1.54	1.97	0.29-13.63	0.491	-	-	-	-	1.93	5.97	0.95-37.42	0.056
▪ 90 day	1.66	2.87	0.52-15.77	0.226	-	-	-	-	2.36	7.79	1.35-44.90	0.022
Hospitalisation												
▪ 30 day	0.73	0.97	0.65-1.44	0.860	1.00	1.21	0.66-2.23	0.532	0.60	0.82	0.49-1.38	0.462
▪ 60 day	0.82	1.08	0.80-1.48	0.613	0.80	0.98	0.61-1.58	0.946	0.84	1.15	0.78-1.70	0.475
▪ 90 day	0.74	0.99	0.74-1.31	0.917	0.78	0.99	0.66-1.48	0.957	0.71	0.98	0.67-1.42	0.902
PCAE												
▪ 30 day	0.87	0.93	0.54-1.60	0.784	0.84	0.84	0.71-1.01	0.056	0.88	0.86	0.75-0.99	0.039
▪ 60 day	0.86	1.01	0.74-1.37	0.970	0.88	0.89	0.79-1.01	0.076	0.85	0.85	0.75-0.95	0.006
▪ 90 day	0.89	1.05	0.84-1.33	0.652	0.93	0.95	0.86-1.06	0.370	0.84	0.83	0.74-0.93	0.001

*Adjustment for confounders listed in table 42 (page 249). Empty cells = inestimable due to lack of exposure in the risk window.

Table 47. Crude and adjusted incidence rate ratios for the association between NSAIDs with <5-fold COX-2 selectivity and asthma events.

Risk window	Any				Incident				Prevalent			
	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value
Death												
▪ 30 day	0.93	1.70	0.22-13.12	0.612	-	-	-	-	1.06	2.11	0.27-16.80	0.479
▪ 60 day	1.13	2.53	0.52-12.25	0.250	-	-	-	-	1.53	4.60	0.62-34.09	0.135
▪ 90 day	1.12	2.26	0.49-10.31	0.293	-	-	-	-	1.37	4.36	0.57-33.52	0.158
Hospitalisation												
▪ 30 day	0.84	0.99	0.71-1.38	0.932	0.80	1.05	0.57-1.95	0.871	0.86	0.96	0.65-1.41	0.824
▪ 60 day	0.77	0.98	0.74-1.30	0.881	0.78	1.07	0.70-1.63	0.754	0.77	0.93	0.65-1.31	0.665
▪ 90 day	0.74	0.93	0.72-1.20	0.591	0.77	1.05	0.74-1.49	0.791	0.71	0.84	0.60-1.18	0.311
PCAE												
▪ 30 day	0.86	0.96	0.56-1.65	0.883	0.87	0.92	0.79-1.08	0.300	0.86	0.87	0.76-0.98	0.027
▪ 60 day	0.90	1.10	0.81-1.51	0.539	0.92	1.00	0.89-1.12	0.957	0.88	0.91	0.82-1.02	0.092
▪ 90 day	0.89	1.13	0.89-1.42	0.315	0.92	1.01	0.92-1.11	0.855	0.86	0.90	0.82-1.00	0.039

*Adjustment for confounders listed in table 42 (page 249). Empty cells = inestimable due to lack of exposure in the risk window.

Table 48. Crude and adjusted incidence rate ratios for the association between NSAIDs with 5-50-fold COX-2 selectivity and asthma events.

Risk window	Any				Incident				Prevalent			
	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value
Death												
▪ 30 day	-	-	-	-	-	-	-	-	-	-	-	-
▪ 60 day	-	-	-	-	-	-	-	-	-	-	-	-
▪ 90 day	-	-	-	-	-	-	-	-	-	-	-	-
Hospitalisation												
▪ 30 day	0.42	0.52	0.18-1.49	0.222	-	-	-	-	0.50	0.60	0.21-1.75	0.351
▪ 60 day	0.60	0.70	0.32-1.52	0.361	-	-	-	-	0.74	0.80	0.36-1.78	0.587
▪ 90 day	0.53	0.66	0.32-1.36	0.260	-	-	-	-	0.69	0.80	0.38-1.70	0.568
PACAE												
▪ 30 day	0.83	0.88	0.49-1.59	0.668	1.08	1.11	0.62-1.98	0.731	0.79	0.76	0.58-1.01	0.057
▪ 60 day	0.82	0.95	0.66-1.37	0.788	0.91	0.94	0.60-1.12	0.770	0.80	0.79	0.62-1.01	0.057
▪ 90 day	0.86	1.01	0.76-1.35	0.937	0.87	0.90	0.62-1.31	0.583	0.85	0.84	0.67-1.06	0.147

*Adjustment for confounders listed in table 42 (page 249). Empty cells = inestimable due to lack of exposure in the risk window.

Table 49. Crude and adjusted incidence rate ratios for the association between COX-2 inhibitors and asthma events.

Risk window	Any				Incident				Prevalent			
	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value	Crude IRR	Adjusted IRR	95% CI	p-value
Death												
▪ 30 day	1.74	2.05	0.15-27.68	0.589	-	-	-	-	1.74	2.57	0.18-36.91	0.488
▪ 60 day	1.29	2.20	0.16-29.62	0.551	-	-	-	-	1.50	5.92	0.30-115.35	0.240
▪ 90 day	0.92	1.39	0.13-15.27	0.786	-	-	-	-	1.02	2.11	0.17-26.84	0.567
Hospitalisation												
▪ 30 day	1.01	0.78	0.41-1.45	0.412	2.26	1.83	0.59-5.65	0.297	0.79	0.55	0.26-1.21	0.137
▪ 60 day	0.99	0.85	0.50-1.45	0.548	1.92	1.31	0.52-3.28	0.566	0.74	0.70	0.367-1.36	0.292
▪ 90 day	0.91	0.83	0.49-1.39	0.474	1.54	1.38	0.63-3.04	0.422	0.65	0.61	0.31-1.21	0.156
PCAE												
▪ 30 day	1.05	1.18	0.67-2.06	0.569	1.02	1.08	0.74-1.58	0.695	1.06	1.09	0.87-1.36	0.452
▪ 60 day	1.01	1.21	0.87-1.69	0.256	1.11	1.17	0.89-1.53	0.267	0.96	1.00	0.82-1.21	0.962
▪ 90 day	1.03	1.25	0.97-1.61	0.079	1.16	1.21	0.97-1.51	0.088	0.94	0.98	0.81-1.19	0.836

*Adjustment for confounders listed in table 42 (page 249). Empty cells = inestimable due to lack of exposure in the risk window.

Overall, there was no significant increase in the relative incidence of PCAE with any type of oral NSAID exposure (incident and prevalent combined, tables 46 to 49). When stratified by duration of administration (incident and prevalent), there was again no significant increase in the relative incidence of PCAE with any class of oral NSAID.

A significant decrease in the relative incidence of PCAE was observed with prevalent exposure to non-selective NSAIDs (IRR 0.86 (95% CI 0.75 to 0.99), 0.85 (95% CI 0.75 to 0.95) and 0.83 (95% CI 0.74 to 0.93) for the 30, 60 and 90 day risk windows respectively, table 46) and NSAIDs with <5-fold COX-2 selectivity (IRR 0.87 (95% CI 0.76 to 0.98), 0.91 (95% CI 0.82 to 1.02) and 0.90 (95% CI 0.82 to 1.00) for the 30, 60 and 90 day risk windows respectively, table 47).

Nested case control sensitivity analyses

Results from sensitivity analyses are presented in tables 50 to 53.

1. Excluding patients hospitalised within the risk period

This was done to assess any impact of immortal time bias. For asthma hospitalisation, this involved excluding 51 (8.8%), 79 (13.6%) and 109 (18.7%) cases for the 30, 60 and 90 day risk windows respectively whilst for PCAE this involved excluding 181 (3.4%), 330 (6.2%) and 498 (9.4%) cases for the 30, 60 and 90 day risk windows respectively. This analysis produced similar results to the main analysis. For incident COX-2 inhibitor exposure, effect estimates were larger for asthma hospitalisation but remained non-significant.

Table 50. Non-selective NSAID sensitivity analyses as per methods.

	Any		Incident		Prevalent	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Hospitalised in risk window						
Hospitalisation						
30 day	0.96	0.63-1.46	1.16	0.60-2.23	0.84	0.49-1.45
60 day	1.10	0.78-1.54	1.08	0.65-1.78	1.11	0.72-1.70
90 day	0.98	0.71-1.34	1.00	0.64-1.56	0.96	0.63-1.46
PCAE						
30 day	0.84	0.74-0.95	0.85	0.71-1.01	0.84	0.73-0.97
60 day	0.85	0.78-0.93	0.88	0.77-1.00	0.83	0.73-0.94
90 day	0.88	0.81-0.96	0.93	0.83-1.04	0.83	0.74-0.94
Diagnosed with asthma ≥ 45						
Hospitalisation						
30 day	1.10	0.69-1.75	1.20	0.59-2.42	1.01	0.55-1.85
60 day	1.10	0.76-1.59	0.90	0.52-1.57	1.26	0.79-2.02
90 day	0.96	0.68-1.35	0.88	0.55-1.41	1.05	0.66-1.65
PCAE						
30 day	0.81	0.70-0.94	0.79	0.64-0.98	0.82	0.67-1.00
60 day	0.83	0.74-0.93	0.83	0.72-0.93	0.82	0.70-0.97
90 day	0.86	0.78-0.96	0.93	0.82-1.05	0.77	0.66-0.91
Smokers over 40 years						
Hospitalisation						
30 day	0.87	0.56-1.35	0.99	0.50-1.96	0.78	0.45-1.37
60 day	0.96	0.68-1.35	0.86	0.51-1.45	1.03	0.66-1.58
90 day	0.88	0.64-1.21	0.88	0.57-1.37	0.88	0.56-1.33
PCAE						
30 day	0.84	0.75-0.95	0.85	0.71-1.03	0.83	0.71-0.97
60 day	0.87	0.79-0.96	0.90	0.79-1.03	0.84	0.74-0.96
90 day	0.90	0.83-0.98	0.97	0.87-1.08	0.82	0.73-0.93
Unmatched on age						
Hospitalisation						
30 day	0.97	0.65-1.44	1.21	0.66-2.23	0.82	0.49-1.38
60 day	1.08	0.80-1.48	0.98	0.61-1.58	1.16	0.78-1.70
90 day	0.99	0.74-1.31	0.99	0.66-1.48	0.98	0.67-1.42
PCAE						
30 day	0.86	0.77-0.96	0.84	0.71-1.00	0.86	0.75-0.99
60 day	0.86	0.79-0.95	0.89	0.79-1.01	0.85	0.75-0.95
90 day	0.90	0.83-0.97	0.95	0.86-1.06	0.83	0.74-0.93
Complete case analysis						
Hospitalisation						
30 day	0.97	0.63-1.50	1.29	0.67-2.48	0.80	0.46-1.41
60 day	1.11	0.80-1.55	0.97	0.58-1.62	1.21	0.80-1.82
90 day	1.04	0.77-1.41	1.00	0.65-1.55	1.07	0.72-1.59
PCAE						
30 day	0.85	0.76-0.96	0.87	0.72-1.04	0.84	0.73-0.98
60 day	0.86	0.79-0.95	0.90	0.79-1.03	0.83	0.73-0.94
90 day	0.89	0.82-0.97	0.95	0.85-1.07	0.83	0.73-0.93

Sensitivity analyses excluding patients: hospitalised within the risk window; smokers >40 years of age; diagnosed with asthma >45 years of age; unmatched on age; complete case analysis.

Table 51. NSAIDs with <5-fold COX-2 selectivity sensitivity analyses as per methods.

	Any		Incident		Prevalent	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Hospitalised in risk window						
Hospitalisation						
30 day	0.99	0.70-1.40	1.19	0.64-2.23	0.92	0.61-1.39
60 day	1.03	0.76-1.39	1.27	0.82-1.97	0.89	0.61-1.31
90 day	0.97	0.73-1.29	1.17	0.80-1.72	0.82	0.56-1.19
PCAE						
30 day	0.88	0.80-0.98	0.91	0.77-1.07	0.87	0.76-0.99
60 day	0.95	0.87-1.03	0.98	0.87-1.10	0.92	0.82-1.02
90 day	0.95	0.86-1.02	0.98	0.89-1.09	0.91	0.82-1.01
Diagnosed with asthma ≥45						
Hospitalisation						
30 day	0.78	0.51-1.20	0.81	0.40-1.68	0.76	0.45-1.28
60 day	0.81	0.57-1.15	0.89	0.55-1.45	0.74	0.47-1.19
90 day	0.80	0.58-1.09	0.95	0.64-1.41	0.66	0.42-1.03
PCAE						
30 day	0.81	0.70-0.92	0.85	0.71-1.03	0.76	0.63-0.92
60 day	0.89	0.81-0.99	0.93	0.82-1.07	0.85	0.73-0.99
90 day	0.91	0.82-1.00	0.96	0.86-1.08	0.83	0.72-0.95
Smokers over 40 years						
Hospitalisation						
30 day	1.02	0.71-1.47	0.92	0.46-1.84	1.05	0.69-1.60
60 day	1.03	0.76-1.40	1.14	0.72-1.80	0.97	0.66-1.43
90 day	0.99	0.75-1.31	1.10	0.75-1.61	0.91	0.63-1.31
PCAE						
30 day	0.91	0.82-1.01	0.96	0.82-1.14	0.88	0.76-1.01
60 day	0.97	0.89-1.05	1.03	0.91-1.16	0.92	0.82-1.03
90 day	0.96	0.89-1.04	1.02	0.92-1.13	0.90	0.81-1.01
Unmatched on age						
Hospitalisation						
30 day	0.99	0.71-1.38	1.05	0.57-1.95	0.96	0.65-1.41
60 day	0.98	0.74-1.30	1.07	0.70-1.63	0.93	0.65-1.31
90 day	0.93	0.72-1.20	1.05	0.74-1.49	0.84	0.60-1.18
PCAE						
30 day	0.89	0.80-0.98	0.92	0.78-1.07	0.87	0.76-0.98
60 day	0.95	0.88-1.03	1.00	0.89-1.11	0.91	0.82-1.01
90 day	0.95	0.89-1.03	1.01	0.91-1.11	0.90	0.82-1.00
Complete case analysis						
Hospitalisation						
30 day	1.07	0.75-1.52	1.26	0.66-2.40	1.00	0.67-1.51
60 day	1.05	0.78-1.41	1.27	0.82-1.97	0.92	0.63-1.34
90 day	1.01	0.77-1.32	1.22	0.84-1.76	0.85	0.59-1.22
PCAE						
30 day	0.90	0.81-1.01	0.97	0.72-1.04	0.86	0.76-0.99
60 day	0.96	0.88-1.04	1.02	0.90-1.14	0.92	0.82-1.02
90 day	0.97	0.90-1.05	1.03	0.93-1.15	0.91	0.82-1.01

Sensitivity analyses excluding patients: hospitalised within the risk window; smokers >40 years of age; diagnosed with asthma >45 years of age; unmatched on age; complete case analysis.

Table 52. NSAIDs with ≥ 5 -fold COX-2 selectivity sensitivity analyses as per methods.

	IRR	Any 95% CI	Incident IRR	Incident 95% CI	Prevalent IRR	Prevalent 95% CI
Hospitalised in risk window						
Hospitalisation						
30 day	0.59	0.21-1.71	-	-	0.76	0.26-2.21
60 day	0.85	0.38-1.88	-	-	0.99	0.44-2.24
90 day	0.73	0.33-1.61	-	-	0.95	0.42-2.15
PCAE						
30 day	0.84	0.65-1.08	1.10	0.62-1.98	0.79	0.59-1.05
60 day	0.85	0.68-1.05	0.98	0.63-1.53	0.81	0.63-1.04
90 day	0.93	0.76-1.14	1.00	0.68-1.45	0.90	0.71-1.14
Diagnosed with asthma ≥ 45						
Hospitalisation						
30 day	0.26	0.03-2.01	-	-	0.34	0.04-2.72
60 day	0.46	0.13-1.60	-	-	0.58	0.16-2.07
90 day	0.53	0.18-1.58	-	-	0.71	0.23-2.19
PCAE						
30 day	0.73	0.48-1.11	1.04	0.44-2.42	0.67	0.42-1.08
60 day	0.79	0.59-1.11	1.00	0.55-1.84	0.71	0.47-1.07
90 day	0.90	0.67-1.23	1.09	0.67-1.78	0.80	0.54-1.18
Smokers over 40 years						
Hospitalisation						
30 day	0.76	0.25-2.30	-	-	0.86	0.28-2.66
60 day	1.00	0.44-2.31	-	-	1.18	0.50-2.77
90 day	0.91	0.42-1.98	-	-	1.16	0.52-2.58
PCAE						
30 day	0.80	0.60-1.07	0.84	0.40-1.75	0.79	0.58-1.08
60 day	0.81	0.63-1.03	0.82	0.49-1.37	0.80	0.61-1.05
90 day	0.84	0.67-1.04	0.77	0.50-1.18	0.86	0.66-1.11
Unmatched on age						
Hospitalisation						
30 day	0.52	0.18-1.49	-	-	0.60	0.21-1.75
60 day	0.70	0.32-1.52	-	-	0.80	0.36-1.78
90 day	0.66	0.62-1.36	-	-	0.80	0.38-1.70
PCAE						
30 day	0.80	0.62-1.04	1.11	0.62-1.98	0.75	0.57-1.00
60 day	0.82	0.66-1.01	0.94	0.60-1.46	0.78	0.61-1.00
90 day	0.86	0.70-1.05	0.90	0.62-1.31	0.83	0.66-1.06
Complete case analysis						
Hospitalisation						
30 day	0.39	0.12-1.31	-	-	0.46	0.14-1.55
60 day	0.62	0.27-1.43	-	-	0.71	0.31-1.66
90 day	0.52	0.23-1.19	-	-	0.63	0.27-1.47
PCAE						
30 day	0.82	0.63-1.07	1.07	0.57-2.01	0.78	0.58-1.04
60 day	0.84	0.67-1.05	0.93	0.59-1.49	0.81	0.62-1.04
90 day	0.88	0.71-1.08	0.87	0.59-1.30	0.87	0.68-1.11

Sensitivity analyses excluding patients: hospitalised within the risk window; smokers >40 years of age; diagnosed with asthma >45 years of age; unmatched on age; complete case analysis.

Table 53. COX-2 inhibitor sensitivity analyses as per methods.

	Any		Incident		Prevalent	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Hospitalised in risk window						
Hospitalisation						
30 day	0.79	0.40-1.55	2.11	0.61-7.39	0.57	0.26-1.29
60 day	1.03	0.59-1.81	1.84	0.69-4.95	0.84	0.41-1.62
90 day	0.98	0.56-1.73	1.59	0.65-3.86	0.75	0.36-1.55
PCAE						
30 day	1.07	0.88-1.31	1.06	0.71-1.57	1.08	0.86-1.35
60 day	1.02	0.86-1.21	1.11	0.84-1.48	0.97	0.80-1.20
90 day	1.08	0.92-1.25	1.19	0.95-1.51	1.00	0.81-1.22
Diagnosed with asthma ≥ 45						
Hospitalisation						
30 day	0.82	0.36-1.86	2.09	0.64-6.88	0.43	0.14-1.36
60 day	0.88	0.43-1.79	1.73	0.62-4.82	0.52	0.19-1.46
90 day	0.81	0.40-1.61	1.23	0.48-3.18	0.54	0.19-1.50
PCAE						
30 day	1.11	0.80-1.53	1.34	0.78-2.33	1.01	0.68-1.50
60 day	1.02	0.78-1.34	1.23	0.82-1.87	0.90	0.63-1.28
90 day	1.06	0.84-1.35	1.14	0.80-1.62	1.00	0.72-1.38
Smokers over 40 years						
Hospitalisation						
30 day	0.87	0.45-1.68	2.39	0.71-8.03	0.62	0.28-1.38
60 day	0.89	0.50-1.57	1.39	0.53-3.63	0.73	0.36-1.47
90 day	0.86	0.50-1.48	1.41	0.63-3.16	0.62	0.30-1.29
PCAE						
30 day	1.09	0.88-1.34	1.09	0.73-1.64	1.09	0.85-1.38
60 day	1.05	0.88-1.25	1.22	0.92-1.63	0.97	0.78-1.21
90 day	1.06	0.90-1.25	1.21	0.96-1.54	0.96	0.78-1.19
Unmatched on age						
Hospitalisation						
30 day	0.77	0.41-1.45	1.81	0.58-5.60	0.55	0.26-1.21
60 day	0.85	0.50-1.45	1.30	0.52-3.25	0.70	0.37-1.36
90 day	0.83	0.49-1.39	1.37	0.62-3.02	0.61	0.31-1.21
PCAE						
30 day	1.09	0.90-1.32	1.08	0.74-1.58	1.09	0.87-1.36
60 day	1.05	0.89-1.24	1.16	0.89-1.52	1.00	0.82-1.22
90 day	1.07	0.93-1.24	1.21	0.97-1.51	0.98	0.81-1.19
Complete case analysis						
Hospitalisation						
30 day	0.76	0.40-1.47	1.82	0.58-5.77	0.54	0.25-1.20
60 day	0.80	0.46-1.39	1.04	0.39-2.78	0.70	0.36-1.37
90 day	0.78	0.45-1.33	1.18	0.51-2.72	0.61	0.30-1.22
PCAE						
30 day	1.09	0.89-1.33	1.06	0.71-1.60	1.09	0.87-1.37
60 day	1.04	0.88-1.23	1.15	0.87-1.53	0.97	0.80-1.20
90 day	1.06	0.91-1.24	1.19	0.94-1.50	0.99	0.81-1.20

Sensitivity analyses excluding patients: hospitalised within the risk window; smokers >40 years of age; diagnosed with asthma >45 years of age; unmatched on age; complete case analysis

2. Excluding patients diagnosed with asthma over the age of 45 years

This was done to assess any impact of including patients who may have unknown fixed airway obstruction. For asthma hospitalisation, this involved excluding 376 (64.5%) of cases whilst for PCAE this involved excluding 2386 (45.0%) of cases. This analysis produced similar results to the main analysis and no significant increases in events were seen with any class of NSAID.

3. Excluding patients over the age of 40 years who smoked

This was done to again assess any impact of including patients who may have unknown fixed airway obstruction. For asthma hospitalisation, this involved excluding 64 (11.0%) of cases whilst for PCAE this involved excluding 688 (13.0%) of cases. This analysis once again produced similar results to the main analysis although the significantly reduced incidence of PCAE associated with non-selective NSAID and NSAIDs with <5-fold COX-2 selectivity became non-significant (tables 9.10 and 9.11).

4. Excluding patients originally unmatched on age

This was done to assess for any residual confounding by age. This only affected 0.1% of cases of PCAE and results were therefore almost identical to those of the main analysis.

5. Complete case analysis

This was done to assess the impact of multiply imputing data on height, weight and smoking status. For asthma hospitalisation, data was missing on height, weight and smoking status for 279 (4.4%), 211 (3.3%) and 396 (6.2%) of people respectively whilst for PCAE data was missing on height, weight and smoking status for 2397 (4.2%), 1971

(3.4%) and 3782 (6.6%) of people respectively. Again this analysis produced very similar results to the main analysis.

9.4.2 Self-controlled case series

The five SCCS consisted of:

- 918 patients (mean age 44.8 years, 66% female) with incident exposure to non-selective NSAID experiencing 2677 PCAEs;
- 1106 patients (mean age 42.6 years, 66% female) with incident exposure to NSAIDs with <5-fold COX-2 selectivity experiencing 3350 PCAEs;
- 44 patients (mean age 51.9 years, 80% female) with incident exposure to NSAIDs with ≥ 5 -fold COX-2 selectivity experiencing 153 PCAEs; and
- 136 patients (mean age 54.4 years, 71% female) with incident exposure to COX-2 inhibitors experiencing 603 PCAEs.

The most common NSAIDs were ibuprofen, diclofenac, meloxicam and celecoxib for each class of NSAID respectively. The number of events, total person time and crude incidence of PCAE for the baseline period, pre-risk period, acute risk period and the chronic risk period is shown in table 54. As expected, the crude incidence of PCAE was lower during the pre-risk periods for all classes of NSAID. The crude and adjusted relative incidence of PCAE associated with oral NSAID exposure is shown in table 55. Overall, no significant increase in the relative incidence of PCAE occurred for any class of NSAID using any acute risk period with any type of exposure. Non-selective NSAIDs were associated with a significant reduced relative incidence of PCAE during the 30 and 90 day acute risk period (IRR 0.76 (95% CI 0.60 to 0.95) and IRR 0.86 (95% CI 0.75 to 0.98) respectively).

Table 54. Crude incidence rates according to class of NSAID, exposure group and risk window.

Risk Period	Non-selective			<5 fold selectivity			5-50 fold selectivity			COX-2 inhibitors		
	Events	Days	Crude Incidence*	Events	Days	Crude Incidence*	Events	Days	Crude Incidence*	Events	Days	Crude Incidence*
Pre-risk	87	27431	31.72	84	32937	25.50	2	1318	15.17	6	4053	14.80
30 day												
Baseline	989	256277	38.59	1189	308721	38.51	50	11171	44.76	140	36131	38.75
Acute	82	27494	29.82	119	33102	35.95	7	1319	53.07	17	4073	41.74
Chronic	75	18399	40.76	73	22307	32.73	4	1904	21.01	16	4548	35.18
60 day												
Baseline	905	234407	38.61	1087	282523	38.47	48	10321	46.51	124	33455	37.06
Acute	185	54922	33.68	244	66236	36.84	11	2638	41.70	39	8140	47.91
Chronic	56	12766	43.87	50	15339	32.60	2	1434	13.95	10	3152	31.73
90 day												
Baseline	824	211346	38.99	986	254638	38.72	43	9451	45.50	113	30370	37.21
Acute	280	82415	33.97	365	99331	36.75	16	3946	40.55	53	12212	43.40
Chronic	42	8307	50.56	30	10052	29.84	2	992	20.16	7	2157	32.45

*Per 10,000 person years.

Table 55. Association between type of NSAID exposure and primary care asthma exacerbations using the self-controlled case series.

Risk Period	Non-selective			<5 fold selectivity			5-50 fold selectivity			COX-2 inhibitors		
	IRR	95% CI	p-value	IRR	95% CI	p-value	IRR	95% CI	p-value	IRR	95% CI	p-value
30 day												
Acute	0.76	0.60-0.95	0.017	0.92	0.76-1.11	0.364	1.33	0.59-2.97	0.494	1.06	0.64-1.76	0.831
Chronic	0.89	0.67-1.18	0.417	0.78	0.59-1.04	0.088	0.69	0.21-2.29	0.544	0.88	0.47-1.66	0.690
60 day												
Acute	0.86	0.73-1.01	0.062	0.94	0.82-1.08	0.377	0.99	0.51-1.94	0.977	1.27	0.88-1.84	0.208
Chronic	0.97	0.70-1.34	0.860	0.77	0.55-1.07	0.118	0.40	0.09-1.89	0.249	0.74	0.35-1.58	0.436
90 day												
Acute	0.86	0.75-0.98	0.027	0.93	0.82-1.05	0.227	0.99	0.54-1.81	0.977	1.14	0.81-1.60	0.461
Chronic	1.12	0.78-1.60	0.559	0.67	0.45-1.01	0.054	0.64	0.14-3.06	0.576	0.69	0.29-1.66	0.412

Adjusted for use of SABA, LABA, ICS, leukotriene receptor antagonists, methylxanthines and seasonal variation.

9.5 Discussion

The aim of this chapter was to assess the adverse respiratory effect of NSAIDs prescribed to people with asthma. These analyses found no strong evidence that oral NSAID exposure was associated with an increase in the incidence of asthma death, hospitalisation and PCAE. Based upon the general understanding around the pathogenesis of reactions in people with AERD, adverse respiratory effects from NSAIDs are more likely to be observed with incident rather than prevalent NSAID exposure. This is because most people issued repeat NSAID prescriptions are likely to have NSAID-tolerant asthma and be at lower risk of asthma morbidity. NSAID-induced reactions are typically thought to occur within the first few hours of ingestion and therefore people who develop respiratory reactions shortly following NSAID exposure are likely to avoid NSAIDs in the future. This may partly explain the reduced relative incidence of PCAE associated with prevalent exposure to non-selective NSAIDs and NSAIDs with <5-fold COX-2 selectivity. However, this would rely upon people correctly attributing respiratory symptoms to NSAID exposure which may not always be the case, especially if symptoms are mild or exposure occurs at the same time as uncontrolled asthma symptoms (such as during a respiratory tract infection). This was shown by a European wide cross-sectional study involving 500 people with AERD which found that only 15% of people became aware of sensitivity to aspirin following a provocation challenge test (98).

Strengths and limitations

Although a significant association with asthma death and prevalent NSAID exposure was observed, it was only significant using a single risk window and effect sizes became smaller when shorter risk windows were applied. It is likely that this association

is non-causal and more related to other factors such as residual confounding or a spurious statistically significant result due to multiple testing. If this association were causal, one would expect similar associations with asthma hospitalisation and PCAE or with incident exposure to be observed. In fact, prevalent non-selective NSAID exposure was associated with a significantly reduced risk of PCAE in the nested case control study.

No increased risk of PCAE was observed with any type of NSAID in the SCCS and was consistent with findings from the nested case control study. The systematic review of clinical trials presented in chapter 5 demonstrates tolerability of COX-2 inhibitors in people with AERD and this study supports this observation. However, no significant increase in events was seen with non-selective NSAIDs. People with AERD are at increased risk of asthma morbidity compared to people with NSAID-tolerant asthma. It is therefore possible that people with AERD or more severe asthma would be prescribed COX-2 inhibitors instead other types of NSAIDs because clinicians thought they were safer. Confounding by indication could therefore affect observational studies comparing the risk from different classes of NSAIDs, since the British National Formulary has long carried a 'blue box' warning of this risk and it is therefore likely to have been widely known among prescribers over the period of this analysis. This is an important consideration for the nested case control study which is a between-person design, but is unlikely to affect the SCCS due to its within person design controlling for all fixed-confounders. Non-causal associations could also occur if there are large differences in clinical indication for COX-2 inhibitors versus other types of NSAIDs which seems unlikely. It was not possible to determine the exact clinical indication for NSAID prescribing in order to make better comparisons to test this assumption. The asthma

analgesic cohort consisted of people prescribed NSAIDs, paracetamol or paracetamol-containing preparations with low dose opiates in an attempt to identify people with broadly similar indications for mild to moderate analgesics. However, NSAIDs are prescribed at step two of the analgesic ladder it is possible that comparisons between people prescribed other types of analgesics may have been better. No attempt was made to determine whether a dose-response relationship exists for NSAIDs because of difficulty in defining the exact dose and the pattern in which patients took their analgesics.

Assessing the risk from oral NSAID prescribing in asthma using observational data is also difficult because oral NSAIDs are available over-the-counter. Incident NSAID exposure was defined as an NSAID being prescribed in the risk window with no exposure in the year before. It is therefore possible that true incident exposure was not being evaluated in some of these people resulting in bias to the null for reasons described above. It has long been recognised that NSAIDs may trigger exacerbations in susceptible people with asthma and UK national asthma guidelines recommend that patients with asthma are asked about NSAID-induced reactions prior to prescribing which is likely to result in selection bias. Most clinicians will therefore avoid prescribing NSAIDs in people with a history of AERD, in those with unknown AERD status, or in those with more severe asthma which would lead to a bias to the null. These factors make it difficult to quantify the true risk of oral NSAID exposure in asthma using electronic health care records from the UK. However, it does suggest that the *current* practice of oral NSAID prescribing to selected people with asthma in the UK is by and large safe.

9.6 Summary

This chapter observed no strong evidence of an increased risk of asthma events with oral NSAIDs prescribed in the community irrespective of selectivity. This analysis is likely to be affected by the way clinicians choose to prescribe NSAIDs to people with asthma in primary care because of historic safety concerns. This results in selection bias, and a bias to the null when performing observational studies quantifying the risk of NSAID exposure in asthma using routinely health care data from the UK. It is therefore not possible to make any general recommendations about how risky NSAIDs are or whether more people could safely be prescribed these agents. This is the last results chapter in this thesis and is followed by the discussion chapter. The discussion chapter will provide an overview of the work presented in this thesis and will attempt to put it into context in terms of clinical implications. It will also discuss several limitations and ways in which different approaches could have been taken. Finally it will discuss the gaps in current evidence and future work.

Chapter 10: Discussion

The aim of this thesis was to evaluate the risk of beta-blockers and NSAIDs in asthma using two different approaches. In the first half of this thesis, three systematic reviews and meta-analyses of clinical trial evidence evaluating acute exposure to beta-blockers and NSAIDs were performed. This was done to synthesize evidence with strong internal validity. In the second half of the thesis new pharmacoepidemiological studies were performed using linked electronic primary care data generating evidence with external validity.

Beta-blockers – systematic review studies

The first chapter in this thesis evaluated acute exposure to beta-blockers using a systematic review and meta-analysis of randomised, blinded placebo-controlled trials (chapter 3). The outcomes in this meta-analysis were mean percentage change in FEV1, falls in FEV1 of 20% or greater, incidence of respiratory symptoms and mean percentage FEV1 response to SABA following beta-blockade.

This meta-analysis found that acute selective beta-blocker exposure caused a mean fall in FEV1 of 7%, statistically significant falls in FEV1 of 20% or greater affecting around 1 in 8 people with asthma, and a non-significant increase in respiratory symptoms affecting 1 in 33 people with asthma. The mean FEV1 response to SABA following acute exposure to selective beta-blockers was blunted by around 10% compared to placebo. Despite this significant blunting, mean FEV1 values increased well beyond baseline levels following acute selective beta-blocker exposure.

In contrast, acute non-selective beta-blocker exposure caused a mean fall in FEV1 of around 10%, a statistically significant increase in respiratory symptoms affecting around

1 in 13 people with asthma and a non-significant increase in falls in FEV1 of 20% or greater affecting around 1 in 9 people with asthma. The mean FEV1 response to SABA following acute exposure to non-selective beta-blockers was blunted by around 20% compared to placebo and mean FEV1 values did not increase beyond baseline levels unlike acute exposure to selective agents.

In the beta-blocker meta-analysis, acute exposure to selective and non-selective beta-blockers both produced similar falls in FEV1 of 20% or greater. This outcome was included because subsets of people more susceptible to the effects of beta-blockade may exist in which evaluation based upon the sole use of mean changes in FEV1 may be misleading. In this regard, a mean fall in FEV1 of 5% for a group could occur either if all patients experience a 5% fall, or if one patient had a fall of 23% and the remaining 9 patients had a fall of 3%, which significantly alters the appreciation of risk. It is therefore possible that the presence of other factors may be important to trigger a clinically significant asthma exacerbation following beta-blockade. Such factors may include uncontrolled airway inflammation in patients not adhering to inhaled corticosteroids resulting in increased airway hyper-responsiveness (AHR) or genetic factors such as the arginine-16 beta2-adrenoceptor polymorphism (Arg-16). Approximately 15% of Caucasian asthmatics possess two copies of the Arg-16 polymorphism which predisposes to asthma exacerbations in people using regular salmeterol in conjunction with ICS (225).

The systematic review also demonstrated that higher doses of selective beta-blockers caused greater mean reductions in FEV1 which is in keeping with a loss of beta1-adrenoceptor selectivity at higher doses. In a study by Nuttal et al. increasing doses of

atenolol caused greater beta2-adrenoceptor blocking activity as defined by changes in serum potassium, glucose and insulin concentrations following an infusion of the beta2-agonist terbutaline (226). The beta-blocker meta-analysis also demonstrated clinically important differences in treatment effect between individual drugs within each class. Acute exposure to celiprolol and labetalol did not cause a significant mean change in FEV1, whilst acute exposure to acebutolol and propranolol caused the largest mean change in FEV1 compared to placebo. Although celiprolol and labetalol appeared to be well tolerated in terms of mean change in FEV1, it was not possible to calculate falls in FEV1 of 20% or greater, incidence of respiratory symptoms, or response to SABA for them because of the lack of data and there was insufficient routine data to perform observational studies specifically looking at these.

The beta-blocker systematic review process found no eligible studies evaluating topical beta-blocker eye drops used for the treatment of glaucoma. It is plausible that risk from topical therapy might be greater than with oral administration because rapid absorption of topical eye drops into the systemic circulation may occur, without undergoing first-pass metabolism in the liver as is the case for orally administered drugs. In this sense, topical beta-blocker eye drops may have similar effects to that of intravenous administration in terms of beta2-adrenoceptor occupancy and cardiopulmonary effects (227). Given the widespread use of topical beta-blockers for glaucoma, the paucity of high quality trials on the safety of these agents in patients with reversible airways disease was surprising.

In summary, this systematic review demonstrates that the adverse respiratory response from beta-blockers in asthma varies according to selectivity and dose of administration.

Although selective beta-blockers are much better tolerated in people with asthma acute exposure at the doses administered is not risk free. The clinical significance of the degree of the blunted response to beta2-agonists with acute selective bet-blocker exposure is uncertain as mean FEV1 values still increased beyond baseline levels.

Beta-blockers – drug utilisation study

The drug utilisation study in chapter 6 found that the prevalence of selective beta-blocker prescribing in people with active asthma increased by around 200% over the 12 year study period, whilst the prevalence of non-selective beta-blocker prescribing in people with active asthma increased by around 90% over this same period. This increase in beta-blocker prescribing to people with active asthma clearly demonstrated a population at risk in which to perform new observational studies.

Beta-blockers – observational pharmacoepidemiology studies

The first of these observational studies evaluated propranolol exposure in a cohort of people with asthma and anxiety using a nested case control study together with all people with active asthma and incident propranolol exposure experiencing a PCAE using the SCCS design (chapter 7). The NCC study found that propranolol exposure was associated with a large statistically significant increase in asthma hospitalisation which primarily related to incident propranolol exposure and high dose propranolol exposure. The SCCS conducted in the same chapter evaluated PCAE as an outcome only and no statistically significant increased risk of PCAE occurred within 30 days of incident propranolol prescribing.

The next chapter evaluated exposure to oral beta-blockers commonly used for the management of CVD using a cohort of people with asthma and CVD, again using a nested case control and SCCS design (chapter 8). This nested case control study found that prevalent high dose non-selective beta-blocker exposure was associated with a statistically significant increased risk of asthma hospitalisation and PCAE. There was also a significantly elevated risk of PCAE associated with incident low to moderate dose non-selective beta-blocker exposure. In this nested case control analysis, various types of exposure could not be properly evaluated such as the association between incident non-selective beta-blocker exposure and asthma hospitalisation due to a lack of power (lack of exposure among the cases). The SCCS in this chapter demonstrated a significantly increased risk of PCAE within 30 days of incident non-selective beta-blocker prescribing. In contrast, there was no significant increase in the relative incidence of any of the asthma outcomes associated with any type of selective beta-blocker exposure or dose using the nested case control study or the SCCS approach.

In summary, these observational studies demonstrated that the adverse respiratory response to beta-blockers in asthma varied according to selectivity, by duration of administration and by dose of administration. In contrast to non-selective beta-blocker exposure, treatment with selective beta-blockers was not associated with a significantly increased risk of adverse respiratory events in people with asthma.

Beta-blockers – clinical implications

The risk from non-selective beta-blockers in these observational studies appeared to be related in part to duration of administration. This may be similar to the effects of beta-blockers in heart failure, whereby acute beta-blocker exposure reduces myocardial

contractility whilst chronic exposure is well tolerated and leads to beta-adrenoceptor up-regulation with beneficial effects on ejection fraction and survival. If a similar adaptive response did occur in people with asthma, the duration of exposure required to develop it could depend on a number of factors including individual response. Studies investigating the chronic effects of non-selective beta-blocker exposure have tended to use a selected population of well controlled mild-to-moderate asthmatics in which non-selective beta-blockers were initiated at low dose and the dose gradually up titrated, often using inhaled muscarinic antagonist cover to prevent bronchoconstriction as a result of unopposed increased cholinergic tone (228). Compared to people in those trials, it is likely that some people in the CPRD active asthma cohort had uncontrolled asthma as a result of unrecognised symptoms meaning beta-blocker exposure is likely to be riskier. In this regard, it may be difficult to identify and exclude these people because formal assessment of AHR and measures of active airway inflammation (such as exhaled breath nitric oxide - FENO) are not routinely performed in primary care.

Perhaps unsurprisingly, prevalent high dose non-selective beta-blocker exposure was associated with an increased risk of asthma hospitalisation and PCAE in the asthma CVD cohort. This apparent increase in asthma events goes against the idea of an adaptive response occurring with chronic beta-blocker exposure in asthma, but the trigger for an adaptive response could be dose related with high doses leading to complete beta₂-adrenoceptor blockade not widely tolerated in people with asthma. In this regard, only a small amount of beta₂-adrenoceptor blockade may be required to trigger improvements in AHR such as that seen with metoprolol in a murine model of asthma (229). Although prevalent low to moderate dose non-selective beta-blocker exposure appeared to be generally well tolerated in the observational studies reported

here, no strong evidence was found to support the hypothesis that chronic non-selective beta-blockade actually improves asthma outcomes. This however is an issue that can only really be examined in well-designed clinical trials.

Although low to moderate dose incident non-selective beta-blocker exposure was associated with a significant increase in PCAE in chapter 8, initiation of low dose non-selective beta-blockers in asthma can be tolerated by some people in keeping with the idea there is a population of susceptible people at higher risk (165, 230). It is uncertain in these observational studies whether gradual beta-blocker dose-titration occurred or whether using inhaled muscarinic antagonist therapy may have reduced risk from non-selective beta-blockers further. Although inhaled muscarinic antagonists have been used to prevent bronchoconstriction following beta-blocker exposure in asthma, they are currently not routinely indicated for the management of asthma. Instead, people from these analyses would have relied upon SABA reliever therapy, efficacy of which was shown to be significantly blunted in the beta-blocker meta-analysis.

Aspirin/NSAIDs – systematic review studies

The systematic review and meta-analysis in chapter 4 estimated the prevalence of AERD and the mean provocative dose triggering adverse respiratory reactions in people with AERD. The prevalence of AERD in asthma was found to be 9% in adults as determined by falls in FEV1 of 20% or greater using blinded, placebo-controlled oral provocation challenge tests and 9.6% as determined using surveys reliant upon self-reported history. In this study, the mean provocative dose of aspirin was around 89 mg which is a clinically recommended dose.

The next systematic review and meta-analysis measured the incidence of respiratory symptoms and changes in FEV1 of 20% or greater from blinded placebo-controlled clinical trials evaluating acute exposure to selective NSAIDs and COX-2 inhibitors in people with AERD (chapter 5). This study found that acute exposure to COX-2 inhibitors did not cause any significant adverse respiratory effects compared to placebo in people with AERD. In contrast a small but statistically significant increased risk of lower respiratory tract reactions occurred with selective NSAIDs in approximately 1 in 13 people with AERD. Despite the apparent safety of COX-2 inhibitors, the drug utilisation study in chapter 6 found that the prevalence of COX-2 inhibitor prescribing to people with active asthma was only 0.3% by 2011.

In summary, AERD is relatively common in people with asthma and may be triggered by clinically relevant doses of aspirin. COX-2 inhibitors were well tolerated in people with AERD but are not routinely prescribed to people with asthma.

Aspirin/NSAIDs - observational pharmacoepidemiology studies

The final study was the nested case control study investigating the adverse respiratory effect of oral NSAIDs and COX-2 inhibitors in a cohort of people with asthma prescribed analgesic medications and a SCCS study using all people with active asthma prescribed incident NSAID exposure experiencing a PCAE. These analyses found no strong evidence that oral NSAID exposure was associated with an increase in asthma events. Although a significant association with asthma death and prevalent NSAID exposure was observed in the nested case control study, this association is likely to be non-causal. This is because a significant increase in the relative incidence of asthma death was observed in only one of the risk windows; no increase in asthma

hospitalisation or PCAE occurred with prevalent NSAID exposure; and no significant increase was found with incident NSAID exposure which is expected to have a greater risk in light of the known pathophysiology. No currently published observational studies were found assessing the risk of NSAID prescribing in asthma in order to compare with the findings from that chapter.

In summary, these observational studies found no strong evidence of an increased risk of asthma events with oral NSAIDs prescribed in the community irrespective of selectivity. However, this analysis is likely to be affected by the way clinicians choose to prescribe NSAIDs to people with asthma in the community because of historic safety concerns.

AERD/NSAIDs – clinical implications

Recommendations in clinical asthma guidelines regarding the safe use of NSAIDs in people with asthma and an unknown AERD phenotype appear to lack specific guidance. Challenge tests are considered the gold standard for confirming AERD in individual people but these are not widely recommended or used in routine clinical practice (2, 101). Meanwhile, regulatory agencies such as the MHRA in the UK and the FDA in the US recommend that all NSAIDs are contraindicated in people with AERD regardless of selectivity, whilst clinical guidelines simply recommend asking people with asthma if they have suffered any adverse respiratory effects from NSAIDs prior to prescribing.

The findings from the systematic review evaluating selective NSAIDs and COX-2 inhibitors in people with AERD found that acute exposure to COX-2 inhibitors appears to be safe, at least when initiated at low doses in stable mild to moderate asthmatics. As

such it could be important to optimise asthma control with preventer therapy such as with ICS or leukotriene receptor antagonists to further reduce the risk of adverse events in this population if concerns remained. Up to 90% of people with AERD demonstrate upper respiratory (nasal) responses to aspirin or non-selective NSAIDs, which do not appear to occur with COX-2 inhibitors. Although not considered as clinically important as potentially life-threatening lower respiratory reactions, nasal reactions in people with asthma do significantly affect quality of life (190, 231). Ultimately, the use of any drug depends upon its risk and benefit. As with other types of NSAIDs, COX-2 inhibitors are associated with an increased cardiovascular risk and an overall risk assessment would need to be made in order avoid unintended consequences in people with asthma (232). As is the case with any medication, the lowest effective dose should be used for the shortest period of time with scheduled medical review. However, given the limitations associated with the NSAID observational study it has not been possible to externally validate the risk of NSAIDs in people with asthma using this data although it does suggest that the current practice of oral NSAID prescribing to people with asthma in the UK is by and large safe.

Limitations and alternative methodological approaches – systematic reviews

The systematic reviews in this thesis could have been improved in several ways. Firstly, only English language publications were included in each systematic review which may have introduced language bias, however this is likely to have a limited effect overall because the number of included studies was relatively large. Secondly, only published data were included in each systematic review which may have introduced reporting bias because not all studies reported all of the outcomes evaluated and additional information was not requested. This may have been overcome by requesting additional information

from the study authors and a decision was made not to do this because many of the included studies were over 15 years old. This process would have been time consuming and probably would have resulted in little additional information being provided. Thirdly, analysing individual patient data would have increased the robustness of the results which were often restricted to the analysis of mean group effects which is a general problem with many systematic reviews and meta-analyses. A meta-analysis of observational studies evaluating risk of exposure was not performed because the number of studies identified on scoping was small and meta-analysis would have been methodologically more complex. As such, it is possible some high quality observational data might have been missed.

Finally, although the meta-analyses in this thesis used subgroup analysis to investigate possible statistical heterogeneity, alternative approaches exist such as meta-regression. Meta-regression is a method for evaluating possible explanations for statistical heterogeneity in a meta-analysis and is used principally to investigate associations between study-level characteristics and treatment effects (233). Meta-regression can help to quantify the extent to which statistical heterogeneity is explained by the study characteristic i.e. the proportion of between study variance explained by the study characteristics is calculated and is presented as the adjusted R^2 (such as exposure to ICS or baseline FEV1 values which could modify risk of beta-blocker exposure or the mean percentage fall in FEV1 which is observed respectively). However, meta-regression looks at observational relationships between study characteristics even if those studies are randomised placebo-controlled trials. As such relationships may not be causal and meta-regression may suffer from confounding, lack of power (with resulting false negatives or type II errors) and bias such as aggregation bias in which relationships

across studies may not represent relationships within studies (the ecological fallacy). Meta-regression can also suffer from lack of power if the number of included studies is low.

Limitations and alternative methodological approaches – observational studies

Observational studies may suffer from residual confounding and bias, which was the rationale for including a clinical trial evidence synthesis as a comparison, although clinical trial evidence is typically done in very selected populations. The primary observational analysis was the nested case control study in which time-varying confounding relating to the exposure of interest and changes in asthma medication could be adjusted for more efficiently than with a traditional cohort analysis. However, the nested case control study may suffer from residual time-fixed confounding due to its between-person design. In contrast, the SCCS is a within-person design that controls for all time-fixed confounding but may still suffer from residual time-varying confounding. Both study designs could therefore suffer from bias and confounding, but the specific types of bias and confounding are likely to be different suggesting that consistency in results using both designs increases the strength of evidence for a causal relationship.

The observational studies in this thesis could have been improved in several ways. The nested case control studies were designed to address confounding by indication and to ensure that controls were sampled using a more representative population. However, this reduced the size of the cohort from which cases and controls were identified thereby affecting the power of the study. For this reason, several types of beta-blocker exposure and doses could not be properly evaluated. The nested case control study used a cohort of people with asthma and anxiety because propranolol is primarily thought to be

prescribed for the management of anxiety in the UK and there is reportedly an association between anxiety and asthma control. This analysis potentially could have been improved by including people with other indications for propranolol and matching cases and controls by their indication in order to increase the power of the study whilst still dealing with the issue of confounding by indication.

Choosing different cohort designs may have introduced bias in these nested case control studies. The NSAID analysis conducted in chapter 9 used a cohort of people with asthma prescribed NSAIDs and other low-strength analgesics because clinical indications for NSAIDs were thought to be poorly recorded in CPRD. However, NSAIDs are traditionally prescribed at step 2 of the analgesic ladder and it may have been appropriate to include people prescribed higher strength analgesic preparations. However, the SCCS generally produced consistent results in terms of PCAE suggesting that any bias may not be influential.

The SCCS studies could also have been improved in several ways. The SCCS approach used in this thesis included people with active asthma receiving incident beta-blocker or NSAID exposure experiencing a PCAE during the observation period (case-exposure approach). It would not have been possible to use a case-exposure approach for asthma death and hospitalisation in this thesis due to the small numbers of people with incident exposure who experienced the event of interest during the observation period. However, this could have been improved by including cases without the exposure of interest in the analysis thus providing additional information relating to baseline incidence and time varying confounders (126).

The choice of outcome in the SCCS was restricted to PCAE due to concerns over event-dependent exposures which are likely to be more severe when beta-blockers cause asthma hospitalisation or death. Although including cases of asthma hospitalisation without the exposure of interest would have made this more feasible, issues relating to event-dependent exposures would have remained. The SCCS method requires that events arise in a non-homogenous Poisson distribution and that observation periods should be independent of when an event occurs. A pre-risk period was included in the analysis to account for short-lived event-dependent exposures which occurred as demonstrated by a reduced incidence of PCAE during this period. A pre-risk period is an approach recommended to deal with short-lived event-dependent exposures in the SCCS and ignoring this approach would have overestimated the relative incidence of events (126). In hindsight it may have been worth investigating the risk of asthma hospitalisation using a pre-risk period as well. More recently, an extension to the SCCS methodology which removes this independence assumption has been proposed and it is possible that implementing this new approach may have allowed a better assessment of asthma hospitalisation and PCAE (234).

Additionally, the observation period was restricted to a period of 1 year. In contrast, a longer study observation period could have been used in order to increase the number of people eligible for the SCCS analysis. However, this would have increased the effect of time-varying confounding relating to the exposure of interest and changing patterns of asthma medication. The SCCS is not recommended for evaluating the effects of chronic exposure, and the SCCS was principally used in this thesis to evaluate the acute risk period. However, chronic exposure was defined in order to partition it from baseline incidence which may otherwise be biased.

Alternative between-person and within-person study designs could have been used to investigate the risk from beta-blockers and NSAIDs in this thesis, such as a cohort analysis using propensity scores and the case-crossover study respectively. Propensity scores use patient covariates to predict the propensity for being prescribed the exposure of interest in an attempt to evaluate how comparable exposed and unexposed groups are. Propensity scores can then be used for confounding adjustment or matching exposed and unexposed patient groups. However, a cohort analysis using propensity scores would still be susceptible to time-varying confounding in relation to the exposure of interest and changing patterns of asthma medication. One approach in dealing with time-dependent confounding in cohort studies is to consider using inverse probability weighted marginal structural models which are used to estimate the effect of an exposure on an outcome if time-varying confounders are themselves affected by the exposure (235). An alternative within-person design is the case-crossover study. Like the SCCS, the case-crossover design uses only cases in order to eliminate time-fixed confounding and control selection bias. The case-crossover design compares the risk of exposure in a time period immediately before the outcome to one or more control time periods in the past using the same individual (236). However, this design is again not thought to be appropriate for investigating chronic conditions or chronic exposures.

Confounding by contraindication is an important type of confounding which could affect the validity of results from these observational studies. Confounding by contraindication occurs when a drug is withheld over concerns it may worsen a person's condition. Prescribing beta-blockers and NSAIDs in asthma is therefore a classic example of this whereby these agents could be prescribed to people with less severe

asthma and with a lower risk of exacerbations. The effect of confounding by contraindication would be to produce a bias to the null or an apparent protective effect which may not actually exist. One way of dealing with this would be to investigate the relationship between beta-blocker and NSAIDs and asthma events at a time when the potential risk was unknown or not widely known. However, this was not possible because these agents have long been known to trigger exacerbations in susceptible people with asthma. This is another rationale for performing the meta-analyses of clinical trial evidence in thesis.

Asthma is a clinical diagnosis based upon history, clinical examination, the presence of reversible or variable airflow obstruction, or results from bronchial provocation challenge tests. In the absence of a single diagnostic test for asthma in primary care it is therefore possible that misdiagnosis may occur potentially affecting the validity of the results. In general, diagnoses within CPRD have high validity with one systematic review reporting an overall median positive predictive value across diagnoses of 89% (range 24 to 100%) with a specific figure for diseases of the respiratory system of 88% (116). A recent study by Quint et al. demonstrated that people with COPD can be accurately identified in CPRD. This study validated COPD recording using questionnaires from general practitioners to gather additional information and compared this to specific clinical codes which demonstrated a positive predictive value approaching 90% (237). In contrast, no such validation study has specifically been performed for asthma recording in CPRD which would be important to strengthen the validity in these results. International Classification of Disease codes recorded as the underlying cause of death (recorded in cause 1, cause 2 or cause 3) were used to define cases of asthma death. This was considered synonymous to part 1a, 1b and 1c of UK

ONS requirements for death registration. However, the linked dataset provided by CPRD contains up to nine recorded causes of death per patient. Additionally, asthma hospitalisation was defined as a code for asthma recorded in the primary position on the discharge script provided by CPRD (main reason for admission). These definitions were chosen in order to increase the validity that a case was a case. As such, it is possible that some cases may not have been included if asthma exacerbations had been recorded in other positions. This would potentially underestimate the incidence of asthma death and asthma hospitalisation among the active asthma cohort (calculated in chapter 6) when compared to national statistics if incidence rates in national statistics are calculated using codes for asthma recorded anywhere in the death certificate or hospital discharge record. Other potentially reasons for discrepancies include inaccuracy in coding, excluding people with other respiratory conditions which may lower the threshold for death and hospitalisation and the representativeness of the CPRD population. Many of the effect estimates had large confidence intervals indicating a lack of precision and that power was lacking to properly evaluate risk associated with certain types of exposures, dose and asthma death. Much larger linked datasets would therefore be required to evaluate these properly.

In an ideal situation, large randomised clinical trials would be performed to answer these questions which are not always ethical or feasible when assessing the adverse effects of medicines, especially if these adverse effects are rare. However, given the findings for selective beta-blockers a clinical safety trial to assess the risk versus benefit in people with asthma who have strong clinical indications is perhaps more justifiable, since there is a plausible case that beta-blockers might have chronic beneficial effects

and the studies reported here are consistent with the risk of some beta-blockers being low enough to be manageable in the right trial design.

Potential further research

This study was unable to evaluate certain types of beta-blocker exposure in people with asthma such as the risk of asthma hospitalisation and asthma death associated with incident exposure because of a lack of power. Unless the size of CPRD was to increase substantially through the incorporation of general practices using EMIS system of electronic medical records, proper evaluation would only be possible by repeating the analyses in other datasets and meta-analysing the results. Such datasets could be created by linking Scottish health care data to the community dispensed Prescribing Information System and Scottish Morbidity Records (SMR) which in future will also contain data from general practices through linkage to the Scottish Primary Care Information Resource (SPIRE). Alternatively, national European datasets could be also be used for this purpose. Indeed, a comparison using dispensed prescription data versus issued prescription data would also be valuable as not all prescriptions for beta-blockers or NSAIDs issued to people with asthma may have been dispensed by the community pharmacist.

The lack of randomised blinded placebo-controlled clinical trials evaluating topical beta-blocker eye drops in people with asthma highlights a potential evidence gap. The systematic review process could be repeated with less strict inclusion criteria in an attempt to identify and assess additional studies evaluating topical beta-blocker exposure irrespective of the quality of their design and risk of bias. It would also be

worth using observational data using a similar approach taken in this thesis to evaluate the risk of asthma exacerbations associated with topical beta-blocker exposure.

People with asthma in the UK are not routinely screened for AERD creating potential prescribing dilemmas for physicians and uncertainties for patients. This in turn results in people with asthma avoiding NSAIDs despite strong clinical indications for their use, the majority of which may not have AERD. Further research evaluating the best method of diagnosing AERD would be helpful especially if this could be readily applied in a primary care setting. Finally, the increasing incidence of asthma exacerbations over the last 12 years is a potential cause for concern and further research is required to investigate the reasons behind this increase and to develop interventions aimed at preventing asthma exacerbations. This may involve determining whether rises are attributable to an increase in the absolute number of people experiencing asthma exacerbations or whether rises are attributable to an increase in the rate of recurrent asthma exacerbations experienced by a subset of people, possibly as a result of poor asthma management or difficulty accessing healthcare services.

Conclusion

The work undertaken in this thesis has demonstrated to me the importance of evaluating different sources of evidence when quantifying the adverse effects of medicines and also to consider ways of challenging findings from observational studies in order to test the validity of results, an approach I will apply in the future.

Most prescribing interventions carry some degree of risk and prescribing beta-blockers to people with asthma is no exception. However, risk from beta-blockers in asthma

should be balanced against the potential benefits which are greatest to people with cardiovascular disease. The beta-blocker meta-analysis demonstrated that selective beta-blockers may trigger significant changes in lung function in people with asthma and that risk appears to be greater with high doses when selectivity may be lost. In general however, risk from initiating beta-blockers in people with asthma appears to be low when using a selective beta-blocker, which could be commenced at low dose and gradually up titrated depending upon tolerability because SABAs still appear to be effective should any respiratory symptoms develop. Although some people with asthma may tolerate acute exposure to non-selective beta-blockers, risk is clearly greater and SABA rescue therapy is less effective suggesting their risk outweighs any potential benefits for existing clinical indications and should be avoided.

Around 9% of people with asthma appear to have AERD which can be triggered by aspirin and other NSAIDs. However, no specific diagnostic test for AERD is available in routine clinical care. The currently available evidence suggests that COX-2 inhibitors appear to be safe in people with AERD whilst selective NSAIDs appear to carry a small risk. Therefore, COX-2 inhibitors could be a suitable alternative in people with AERD or in those people with asthma who are unwilling to accept the risk of incident NSAID exposure when testing for AERD is not routinely available. However, limitations of observational data make it difficult to assess the generalizability of these findings.

Publications and presentations

Publications

Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: Meta-analysis of controlled clinical trials. *J Allergy Clin Immunol*. 2014;134(1):40-5.

<http://www.jacionline.org/article/S0091-6749%2813%2901774-0/abstract>

Morales DR, Jackson C, Lipworth BJ, Donnan PT, Guthrie B. Adverse respiratory effect of acute β -blocker exposure in asthma: a systematic review and meta-analysis of randomized controlled trials. *Chest*. 2014;145(4):779-86.

<http://journal.publications.chestnet.org/article.aspx?articleid=1767055>

Conference Presentations

Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH . Prevalence of aspirin-exacerbated respiratory disease: meta-analysis of controlled clinical trials. World Congress of Epidemiology. Anchorage, Aug 2014 (poster presentation).

Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH . Acute NSAID exposure in asthma: meta-analysis of clinical trials. Society for Academic Primary Care Annual Conference, Nottingham; Jul 2013 (oral presentation).

Morales DR, Jackson C, Lipworth BJ, Donnan PT, Guthrie B. Acute β -blocker exposure in asthma: meta-analysis of clinical trials. Society for Academic Primary Care Annual Conference, Nottingham; Jul 2013 (oral presentation).

Morales DR, Jackson C, Lipworth BJ, Donnan PT, Guthrie B. Acute β -blocker exposure in asthma: meta-analysis of clinical trials. International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Montreal; Aug 2013 (poster presentation).

Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH . Acute NSAID exposure in asthma: meta-analysis of clinical trials. International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Montreal; Aug 2013 (poster presentation).

References

1. Global initiative for asthma [Internet]. Global strategy for asthma management and prevention. <http://www.ginasthma.org/>.(accessed 31Sep 2011).
2. British Thoracic Society Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. *Thorax*. 2008;63(Suppl 4):iv1e121.
3. Sakula A. Henry Hyde Salter (1823-71): a biographical sketch. *Thorax*. 1985 Dec;40(12):887-8.
4. Burke W, Fesinmeyer M, Reed K, Hampson L, Carlsten C. Family history as a predictor of asthma risk. *Am J Prev Med*. 2003 Feb;24(2):160-9.
5. Vernon MK, Wiklund I, Bell JA, Dale P, Chapman KR. What do we know about asthma triggers? a review of the literature. *J Asthma*. 2012 Dec;49(10):991-8.
6. Fahy JV, Locksley RM. The airway epithelium as a regulator of Th2 responses in asthma. *Am J Respir Crit Care Med*. 2011 Aug 15;184(4):390-2.
7. Jahnsen FL, Moloney ED, Hogan T, Upham JW, Burke CM, Holt PG. Rapid dendritic cell recruitment to the bronchial mucosa of patients with atopic asthma in response to local allergen challenge. *Thorax*. 2001 Nov;56(11):823-6.
8. Holgate ST. Pathophysiology of asthma: what has our current understanding taught us about new therapeutic approaches? *J Allergy Clin Immunol*. 2011 Sep;128(3):495-505.
9. Kato M, Ishioka T, Kita H, Kozawa K, Hayashi Y, Kimura H. Eosinophil granular proteins damage bronchial epithelial cells infected with respiratory syncytial virus. *Int Arch Allergy Immunol*. 2012;158 Suppl 1:11-8.
10. Martinez FD, Vercelli D. Asthma. *Lancet*. 2013 Oct 19;382(9901):1360-72.
11. Barnes PJ. Pathophysiology of asthma. *Br J Clin Pharmacol*. 1996 Jul;42(1):3-10.
12. James AL, Elliot JG, Jones RL, Carroll ML, Mauad T, Bai TR, et al. Airway smooth muscle hypertrophy and hyperplasia in asthma. *Am J Respir Crit Care Med*. 2012 May 15;185(10):1058-64.
13. Black JL, Panettieri RA, Jr., Banerjee A, Berger P. Airway smooth muscle in asthma: just a target for bronchodilation? *Clin Chest Med*. 2012 Sep;33(3):543-58.
14. Canning BJ, Fischer A. Neural regulation of airway smooth muscle tone. *Respir Physiol*. 2001 Mar;125(1-2):113-27.
15. Brannan JD. Bronchial hyperresponsiveness in the assessment of asthma control: Airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest*. 2010 Aug;138(2 Suppl):11S-7S.
16. Cockcroft DW. Direct challenge tests: Airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest*. 2010 Aug;138(2 Suppl):18S-24S.
17. Hunter CJ, Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID. A comparison of the validity of different diagnostic tests in adults with asthma. *Chest*. 2002 Apr;121(4):1051-7.

18. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet*. 2002 Nov 30;360(9347):1715-21.
19. Smith AD, Cowan JO, Brassett KP, Filsell S, McLachlan C, Monti-Sheehan G, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med*. 2005 Aug 15;172(4):453-9.
20. Townshend J, Hails S, McKean M. Diagnosis of asthma in children. *BMJ*. 2007 Jul 28;335(7612):198-202.
21. Halder P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. 2008 Aug 1;178(3):218-24.
22. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*. 2010 Feb 15;181(4):315-23.
23. Good JT, Jr., Kolakowski CA, Groshong SD, Murphy JR, Martin RJ. Refractory asthma: importance of bronchoscopy to identify phenotypes and direct therapy. *Chest*. 2012 Mar;141(3):599-606.
24. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy*. 2004 May;59(5):469-78.
25. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006 Aug 26;368(9537):733-43.
26. Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2009 Jun;64(6):476-83.
27. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2007 Sep;62(9):758-66.
28. Punekar YS, Sheikh A. Establishing the incidence and prevalence of clinician-diagnosed allergic conditions in children and adolescents using routinely collected data from general practices. *Clin Exp Allergy*. 2009 Aug;39(8):1209-16.
29. Osman M, Hansell AL, Simpson CR, Hollowell J, Helms PJ. Gender-specific presentations for asthma, allergic rhinitis and eczema in primary care. *Prim Care Respir J*. 2007 Feb;16(1):28-35.
30. The Scottish Public Health Observatory [Internet]. Asthma: primary care data. <http://www.scotpho.org.uk/health-wellbeing-and-disease/asthma/data/primary-care> (accessed 1 Sep 2014).
31. Centres for Disease Control and Prevention [Internet]. Asthma. <http://www.cdc.gov/nchs/fastats/asthma.htm> (accessed 1 Sep 2014).
32. Asthma UK [Internet]. Asthma facts and FAQs. <http://www.asthma.org.uk/asthma-facts-and-statistics> (accessed 1 Sep 2014).

33. Hoskins G, McCowan C, Neville RG, Thomas GE, Smith B, Silverman S. Risk factors and costs associated with an asthma attack. *Thorax*. 2000 Jan;55(1):19-24.
34. Bedouch P, Marra CA, FitzGerald JM, Lynd LD, Sadatsafavi M. Trends in asthma-related direct medical costs from 2002 to 2007 in British Columbia, Canada: a population based-cohort study. *PLoS One*. 2012;7(12):e50949.
35. Ismaila AS, Sayani AP, Marin M, Su Z. Clinical, economic, and humanistic burden of asthma in Canada: a systematic review. *BMC Pulm Med*. 2013;13(1):70.
36. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. *J Allergy Clin Immunol*. 2011 Jan;127(1):145-52.
37. Morrison DS, McLoone P. Changing patterns of hospital admission for asthma, 1981-97. *Thorax*. 2001 Sep;56(9):687-90.
38. Strid JM, Gammelager H, Johansen MB, Tonnesen E, Christiansen CF. Hospitalization rate and 30-day mortality among patients with status asthmaticus in Denmark: a 16-year nationwide population-based cohort study. *Clin Epidemiol*. 2013;5:345-55.
39. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. *NCHS Data Brief*. 2012 May(94):1-8.
40. The Scottish Public Health Observatory [Internet]. Asthma: secondary care data. <http://www.scotpho.org.uk/health-wellbeing-and-disease/asthma/data/secondary-care> (accessed 1 Sep 2014).
41. Krishnan V, Diette GB, Rand CS, Bilderback AL, Merriman B, Hansel NN, et al. Mortality in patients hospitalized for asthma exacerbations in the United States. *Am J Respir Crit Care Med*. 2006 Sep 15;174(6):633-8.
42. Roberts NJ, Lewsey JD, Gillies M, Briggs AH, Belozeroff V, Globe DR, et al. Time trends in 30 day case-fatality following hospitalisation for asthma in adults in Scotland: a retrospective cohort study from 1981 to 2009. *Respir Med*. 2013 Aug;107(8):1172-7.
43. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. *Respir Med*. 2007 Aug;101(8):1659-64.
44. Watson L, Turk F, Rabe KF. Burden of asthma in the hospital setting: an Australian analysis. *Int J Clin Pract*. 2007 Nov;61(11):1884-8.
45. The Scottish Public Health Observatory [Internet]. Asthma: mortality data. <http://www.scotpho.org.uk/health-wellbeing-and-disease/asthma/data/mortality-data> (accessed 1 Sep 2014).
46. Weber EJ, Silverman RA, Callahan ML, Pollack CV, Woodruff PG, Clark S, et al. A prospective multicenter study of factors associated with hospital admission among adults with acute asthma. *Am J Med*. 2002 Oct 1;113(5):371-8.
47. Hsiao HJ, Wang LC, Yang YH, Lee JH, Yu HH, Lin YT, et al. A nationwide survey of the severity, comorbidity, and mortality of hospitalized patients with asthma in Taiwan. *Pediatr Neonatol*. 2013 Aug;54(4):254-60.

48. Caminati M, Bettoncelli G, Magnoni MS, Rizzi A, Testi R, Passalacqua G, et al. The level of control of mild asthma in general practice: an observational community-based study. *J Asthma*. 2014 Feb;51(1):91-6.
49. Murphy VE, Clifton VL, Gibson PG. The effect of cigarette smoking on asthma control during exacerbations in pregnant women. *Thorax*. 2010 Aug;65(8):739-44.
50. Westergaard C, Porsbjerg C, Backer V. The effect of smoking cessation on airway inflammation in young asthma patients. *Clin Exp Allergy*. 2014 Nov 28;44(3):353-61.
51. Sims M, Maxwell R, Gilmore A. Short-term impact of the smokefree legislation in England on emergency hospital admissions for asthma among adults: a population-based study. *Thorax*. 2013 Jul;68(7):619-24.
52. Grammer LC, Weiss KB, Pedicano JB, Kimmel LG, Curtis LS, Catrambone CD, et al. Obesity and asthma morbidity in a community-based adult cohort in a large urban area: the Chicago Initiative to Raise Asthma Health Equity (CHIRAH). *J Asthma*. 2010 Jun;47(5):491-5.
53. Camargo CA, Jr., Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med*. 1999 Nov 22;159(21):2582-8.
54. Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. *BMJ*. 2000 Mar 25;320(7238):827-32.
55. Goeman DP, Abramson MJ, McCarthy EA, Zubrinich CM, Douglass JA. Asthma mortality in Australia in the 21st century: a case series analysis. *BMJ Open*. 2013;3(5).
56. Royal College of Physicians [Internet]. Why asthma still kills The National Review of Asthma Deaths (NRAD). 2014. <https://www.rcplondon.ac.uk/sites/default/files/why-asthma-still-kills-full-report.pdf> (accessed 1 Sep 2014).
57. Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med*. 1992 Feb 20;326(8):501-6.
58. Adams NP, Bestall JB, Malouf R, Lasserson TJ, Jones PW. Inhaled beclomethasone versus placebo for chronic asthma. *Cochrane Database Syst Rev*. 2005(1):CD002738.
59. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med*. 2000 Aug 3;343(5):332-6.
60. Waalkens HJ, Van Essen-Zandvliet EEFAUH, M D, Hughes MDFAUG, Gerritsen JFAUD, E J, et al. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. The Dutch CNSLD Study Group. *Am Rev Respir Dis*. 1993 Nov;148(5):1252-7.
61. Kuan YC, How SH, Azian AA, Liam CK, Ng TH, Fauzi AR. Bone mineral density in asthmatic patients on inhaled corticosteroids in a developing country. *Ann Thorac Med*. 2012 Apr;7(2):69-73.

62. Mori H, Tanaka H, Ohno Y, Ito F, Funaguchi N, Endo J, et al. Effect of intermittent systemic corticosteroid on bone metabolism in bronchial asthma patients. *J Asthma*. 2009 Mar;46(2):142-6.
63. Dam TT, Harrison S, Fink HA, Ramsdell J, Barrett-Connor E. Bone mineral density and fractures in older men with chronic obstructive pulmonary disease or asthma. *Osteoporos Int*. 2010 Aug;21(8):1341-9.
64. Weatherall M, James K, Clay J, Perrin K, Masoli M, Wijesinghe M, et al. Dose-response relationship for risk of non-vertebral fracture with inhaled corticosteroids. *Clin Exp Allergy*. 2008 Sep;38(9):1451-8.
65. Lipworth BJ. Antagonism of long-acting beta2-adrenoceptor agonism. *Br J Clin Pharmacol*. 2002 Sep;54(3):231-45.
66. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006 Jan;129(1):15-26.
67. Price D, Musgrave SD, Shepstone L, Hillyer EV, Sims EJ, Gilbert RF, et al. Leukotriene antagonists as first-line or add-on asthma-controller therapy. *N Engl J Med*. 2011 May 5;364(18):1695-707.
68. Chruscinski A, Brede ME, Meinel L, Lohse MJ, Kobilka BK, Hein L. Differential distribution of beta-adrenergic receptor subtypes in blood vessels of knockout mice lacking beta(1)- or beta(2)-adrenergic receptors. *Mol Pharmacol*. 2001 Nov;60(5):955-62.
69. Bossard F, Silantieff E, Lavazais-Blancou E, Robay A, Sagan C, Rozec B, et al. beta1, beta2, and beta3 adrenoceptors and Na⁺/H⁺ exchanger regulatory factor 1 expression in human bronchi and their modifications in cystic fibrosis. *Am J Respir Cell Mol Biol*. 2011 Jan;44(1):91-8.
70. Frishman WH. beta-Adrenergic blockers: a 50-year historical perspective. *Am J Ther*. 2008 Nov-Dec;15(6):565-76.
71. Wright P. Untoward effects associated with practolol administration: oculomucocutaneous syndrome. *Br Med J*. 1975 Mar 15;1(5958):595-8.
72. Baker JG. The selectivity of beta-adrenoceptor antagonists at the human beta1, beta2 and beta3 adrenoceptors. *Br J Pharmacol*. 2005 Feb;144(3):317-22.
73. Heidenreich PA, McDonald KM, Hastie T, Fadel B, Hagan V, Lee BK, et al. Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina. *JAMA*. 1999 May 26;281(20):1927-36.
74. Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999 Jun 26;318(7200):1730-7.
75. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH. Beta-blockers for hypertension. *Cochrane Database Syst Rev*. 2012;11:CD002003.
76. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev*. 2004(2):CD003225.
77. Vass C, Hirn C, Sycha T, Findl O, Bauer P, Schmetterer L. Medical interventions for primary open angle glaucoma and ocular hypertension. *Cochrane Database Syst Rev*. 2007(4):CD003167.

78. Xamoterol in severe heart failure. The Xamoterol in Severe Heart Failure Study Group. *Lancet*. 1990 Jul 7;336(8706):1-6.
79. The Scottish Intercollegiate Guideline Network [Internet]. Management of chronic heart failure. SIGN guideline No. 95. <http://signacuk/guidelines/fulltext/95/indexhtml> (accessed 1 Sep 2014).
80. Haber HL, Simek CL, Gimple LW, Bergin JD, Subbiah K, Jayaweera AR, et al. Why do patients with congestive heart failure tolerate the initiation of beta-blocker therapy? *Circulation*. 1993 Oct;88(4 Pt 1):1610-9.
81. McNeill RS, Ingram CG. Effect of propranolol on ventilatory function. *Am J Cardiol*. 1966 Sep;18(3):473-5.
82. Spitz DJ. An unusual death in an asthmatic patient. *Am J Forensic Med Pathol*. 2003 Sep;24(3):271-2.
83. Jones K, Berrill WT, Bromly CL, Hendrick DJ. A confidential enquiry into certified asthma deaths in the North of England, 1994-96: influence of co-morbidity and diagnostic inaccuracy. *Respir Med*. 1999 Dec;93(12):923-7.
84. Morales DR, Guthrie B, Lipworth BJ, Donnan PT, Jackson C. Prescribing of beta-adrenoceptor antagonists in asthma: an observational study. *Thorax*. 2011 Jun;66(6):502-7.
85. Olenchok BA, Fonarow GG, Pan W, Hernandez A, Cannon CP. Current use of beta blockers in patients with reactive airway disease who are hospitalized with acute coronary syndromes. *Am J Cardiol*. 2009 Feb 1;103(3):295-300.
86. Chen J, Radford MJ, Wang Y, Marciniak TA, Krumholz HM. Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma. *J Am Coll Cardiol*. 2001 Jun 1;37(7):1950-6.
87. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for reversible airway disease. *Cochrane Database Syst Rev*. 2002(4):CD002992.
88. Brooks TW, Creekmore FM, Young DC, Asche CV, Oberg B, Samuelson WM. Rates of hospitalizations and emergency department visits in patients with asthma and chronic obstructive pulmonary disease taking beta-blockers. *Pharmacotherapy*. 2007 May;27(5):684-90.
89. Barnett MJ, Milavetz G, Kaboli PJ. beta-Blocker therapy in veterans with asthma or chronic obstructive pulmonary disease. *Pharmacotherapy*. 2005 Nov;25(11):1550-9.
90. Babu KS, Salvi SS. Aspirin and asthma. *Chest*. 2000 Nov;118(5):1470-6.
91. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. *Proc Natl Acad Sci U S A*. 1999 Jun 22;96(13):7563-8.
92. National Institute for Health and Clinical Excellence [Internet]. Osteoarthritis. NICE clinical guideline 59. London: National Institute for Health and Clinical Excellence. <http://www.nice.org.uk/guidance/cg177>. (accessed 1 Sep 2014).
93. Zhou Y, Boudreau DM, Freedman AN. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. *Pharmacoepidemiol Drug Saf*. 2014 Jan;23(1):43-50.

94. Stevenson DD. Aspirin sensitivity and desensitization for asthma and sinusitis. *Curr Allergy Asthma Rep.* 2009 Mar;9(2):155-63.
95. Gaber F, Daham K, Higashi A, Higashi N, Gulich A, Delin I, et al. Increased levels of cysteinyl-leukotrienes in saliva, induced sputum, urine and blood from patients with aspirin-intolerant asthma. *Thorax.* 2008 Dec;63(12):1076-82.
96. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis and management. *J Allergy Clin Immunol.* 1999 Jul;104(1):5-13.
97. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ.* 2004 Feb 21;328(7437):434.
98. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J.* 2000 Sep;16(3):432-6.
99. McDonald JR, Mathison DA, Stevenson DD. Aspirin intolerance in asthma. Detection by oral challenge. *J Allergy Clin Immunol.* 1972 Oct;50(4):198-207.
100. Picado C, Castillo JA, Montserrat JM, Agusti-Vidal A. Aspirin-intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation. *Eur Respir J.* 1989 Feb;2(2):127-9.
101. National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program [Internet]. Guidelines for the Diagnosis and Management of Asthma. 2007. <http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/> (accessed 1 Sep 2014).
102. Thomas M, von Ziegenweidt J, Lee AJ, Price D. High-dose inhaled corticosteroids versus add-on long-acting beta-agonists in asthma: an observational study. *J Allergy Clin Immunol.* 2009 Jan;123(1):116-21 e10.
103. Food and Drug Administration [Internet]. Highlights of prescribing information for celecoxib. 2008. http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020998s0271b1.pdf (accessed 1 Sep 2014).
104. Medicines and Healthcare products Regulatory Agency [Internet]. Medicines Information: Product details celecoxib. 2008. <http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/?prodName=CELEBREX%20200MG&subsName=CELECOXIB&pageID=SecondLevel> (accessed 1 Sep 2014).
105. Gyllfors P, Bochenek G, Overholt J, Drupka D, Kumlin M, Sheller J, et al. Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgetic drug celecoxib. *J Allergy Clin Immunol.* 2003 May;111(5):1116-21.
106. Deeks JJ, Higgins, J. P. T. Statistical algorithms in Review Manager 5. <https://tech.cochrane.org/revman/documentation/Statistical-methods-in-RevMan-5.pdf> 2010;(accessed 1 Sep 2014).
107. Deeks JJ, Higgins, J. P. T., Altman, D. G. Chapter 9: Analysing data and undertaking meta-analyses. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* <http://handbook.cochrane.org/>. 2008;(accessed 1 Sep 2014).

108. Deeks JJ, Higgins, J. P. T., Altman, D. G. Chapter 16: Special topics in statistics. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. <http://handbookcochraneorg/> 2011;(accessed 1 Sep 2014).
109. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol.* 2005;5:13.
110. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol.* 2002 Feb;31(1):140-9.
111. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
112. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997 Sep 13;315(7109):629-34.
113. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009 Jul 21;6(7):e1000097.
114. Health and Social Care Information Centre [Internet]. Read Codes. . <http://systemshscicgovuk/data/uktc/readcodes> (accessed 1 Sep 2014).
115. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract.* 2010 Mar;60(572):e128-36.
116. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol.* 2010 Jan;69(1):4-14.
117. Health and Social Care Information Centre [Internet]. Hospital Episode Statistics. <http://wwwhscicgovuk/hes> (accessed 1 Sep 2014).
118. Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press. <http://www.medicinescomplete.com> (accessed 1 Sep 2014).
119. Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. *FASEB J.* 2004 May;18(7):790-804.
120. Etminan M, Samii A. Pharmacoepidemiology I: a review of pharmacoepidemiologic study designs. *Pharmacotherapy.* 2004 Aug;24(8):964-9.
121. Etminan M. Pharmacoepidemiology II: the nested case-control study--a novel approach in pharmacoepidemiologic research. *Pharmacotherapy.* 2004 Sep;24(9):1105-9.
122. British Columbia Ministry of Health [Internet]. Heart Failure Care. 2008. http://www.bcguidelines.ca/guideline_heart_failure_care.html (accessed 1 Sep 2014).
123. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Fam Pract.* 2010;11:1.
124. Marston L, Carpenter JR, Walters KR, Morris RW, Nazareth I, Petersen I. Issues in multiple imputation of missing data for large general practice clinical databases. *Pharmacoepidemiol Drug Saf.* 2010 Jun;19(6):618-26.

125. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res.* 2007 Jun;16(3):219-42.
126. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med.* 2006 May 30;25(10):1768-97.
127. National Institute for Health and Clinical Excellence [Internet]. Hypertension in pregnancy. NICE clinical guideline 107. London: National Institute for Health and Clinical Excellence. . <http://www.nice.org.uk/guidance/cg107> (accessed 1 Sep 2014).
128. Benson MK, Berrill WT, Cruickshank JM, Sterling GS. A comparison of four beta-adrenoceptor antagonists in patients with asthma. *Br J Clin Pharmacol.* 1978 May;5(5):415-9.
129. Beumer HM, Teirlinck C, Wiseman RA. Comparative investigation of the respiratory and cardiovascular effect of mepindolol, propranolol and pindolol in asthmatic patients. *Int J Clin Pharmacol Biopharm.* 1978 Jun;16(6):249-53.
130. Boye NP, Vale JR. Effect in bronchial asthma of a new beta-adrenergic blocking drug atenolol (ICI 66, 082). *Eur J Clin Pharmacol.* 1977;11(1):11-4.
131. Cannon RE, Slavin RG, Gonasun LM. The effect on asthma of a new beta blocker, pindolol. *Am Heart J.* 1982;104(2 II):438-42.
132. Chatterjee SS. The cardioselective and hypotensive effects of bisoprolol in hypertensive asthmatics. *J Cardiovasc Pharmacol.* 1986;8 Suppl 11:S74-7.
133. Chodosh S, Tuck J, Blasucci DJ. The effects of dilevalol, metoprolol, and placebo on ventilatory function in asthmatics. *J Cardiovasc Pharmacol.* 1988;11 Suppl 2:S18-24.
134. Dal Negro RW, Tognella S, Micheletto C. Pharmacokinetics of the effect of nebivolol 5mg on airway patency in patients with mild to moderate bronchial asthma and arterial hypertension: A randomised, placebo-controlled study. *Clinical Drug Investigation.* 2002;22(3):197-204.
135. Devereux G, Fishwick K, Aiken TC, Bourke SJ, Hendrick DJ. Adverse effects of a single dose of (+)-sotalol in patients with mild stable asthma. *Br J Clin Pharmacol.* 1998 Jul;46(1):79-82.
136. Doshan HD, Brown R, Applin WJ, Kapoor M, Caruso FS. Effects of high doses of celiprolol in asthmatic patients. *J Cardiovasc Pharmacol.* 1986;8 Suppl 4:S109-11.
137. Doshan HD, Rosenthal RR, Brown R, Slutsky A, Applin WJ, Caruso FS. Celiprolol, atenolol and propranolol: a comparison of pulmonary effects in asthmatic patients. *J Cardiovasc Pharmacol.* 1986;8 Suppl 4:S105-8.
138. Ellis ME, Sahay JN, Chatterjee SS, Cruickshank JM, Ellis SH. Cardioselectivity of atenolol in asthmatic patients. *Eur J Clin Pharmacol.* 1981;21(3):173-6.
139. Ellis ME, Hussain M, Webb AK, Barker NP, Fitzsimons TJ. The effect of cimetidine on the relative cardioselectivity of atenolol and metoprolol in asthmatic patients. *Br J Clin Pharmacol.* 1984;17 Suppl 1:59S-64S.
140. Falliers CJ, Vrchota J, Blasucci DJ, Maloy JW, Medakovic M. The effects of treatments with labetalol and hydrochlorothiazide on ventilatory function of asthmatic hypertensive patients with demonstrated bronchosensitivity to propranolol. *J Clin Hypertens.* 1985 Mar;1(1):70-9.

141. Falliers CJ, Vincent ME, Medakovic M. Effect of single doses of labetalol, metoprolol, and placebo on ventilatory function in patients with bronchial asthma: interaction with isoproterenol. *J Asthma*. 1986;23(5):251-60.
142. Fogari R, Zoppi A, Tettamanti F, Poletti L, Rizzardi G, Fiocchi G. Comparative effects of celiprolol, propranolol, oxprenolol, and atenolol on respiratory function in hypertensive patients with chronic obstructive lung disease. *Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy*. 1990(4):1145-9.
143. Jackson SH, Beevers DG. Comparison of the effects of single doses of atenolol and labetalol on airways obstruction in patients with hypertension and asthma. *Br J Clin Pharmacol*. 1983 May;15(5):553-6.
144. Lammers JW, Folgering HT, van Herwaarden CL. Ventilatory effects of atenolol and bevantolol in asthma. *Clin Pharmacol Ther*. 1985 Oct;38(4):428-33.
145. Larsson K. Influence of labetalol, propranolol and practolol in patients with asthma. *Eur J Respir Dis*. 1982 May;63(3):221-30.
146. Lawrence DS, Sahay JN, Chatterjee SS, Cruickshank JM. Asthma and beta-blockers. *Eur J Clin Pharmacol*. 1982;22(6):501-9.
147. Lofdahl CG, Svedmyr N. Cardioreslectivity of atenolol and metoprolol. A study in asthmatic patients. *Eur J Respir Dis*. 1981(6):396-404.
148. Lofdahl CG, Dahlof C, Westergren G, Olofsson B, Svedmyr N. Controlled-release metoprolol compared with atenolol in asthmatic patients: interaction with terbutaline. *Eur J Clin Pharmacol*. 1988;33 Suppl:S25-32.
149. Matthys H, Doshan HD, Ruhle KH, Braig H, Pohl M, Applin WJ, et al. The bronchosparring effect of celiprolol, a new beta 1- alpha 2-receptor antagonist on pulmonary function of propranolol-sensitive asthmatics. *J Clin Pharmacol*. 1985 Jul-Aug;25(5):354-9.
150. Mue S, Sasaki T, Ohmi T. Influence of acebutolol on the haemodynamic and respiratory function of asthmatic patients. *Journal of Pharmacotherapy*. 1979;2(2):67-71.
151. Nair S, Maguire WC, Laddu AR. The effect of acebutolol, a beta adrenergic blocking agent, and placebo on pulmonary functions in asthmatics. *International Journal of Clinical Pharmacology Therapy and Toxicology*. [Journal]. 1981;19(12):519-26.
152. Nicolaescu V, Manicatide M, Stroescu V. -Adrenergic blockade with practolol in acetylcholine-sensitive asthma patients. *Respiration*. 1972;29(2):139-54.
153. Nicolaescu V, Racoveanu C, Manicatide M. Effects of exercise on practolol-treated asthmatic patients. *Eur J Clin Pharmacol*. 1973 Jun;6(1):3-8.
154. Repsher LH, Vincent ME, Medakovic M. The effect of single doses of labetalol, metoprolol and placebo on ventilatory function in patients with bronchial asthma. *J Hypertens*. 1986(Suppl. 5):S510-s2.
155. Skinner C, Gaddie J, Palmer KN. Comparison of intravenous AH 5158 (ibidomide) and propranolol in asthma. *Br Med J*. 1975(5962):59-61.
156. Sue DY, Hansen JE, Wasserman K. The value of exercise in testing beta blockade and airway reactivity in asthmatic patients. *Am Heart J*. 1982 Aug;104(2 Pt 2):442-5.

157. Suzuki S, Mue S, Ohmi T. Effect of atenolol on pulmonary function in asthma. *Acta Therapeutica. [Journal]*. 1981;7(1):55-65.
158. Tantucci C BB, Dottorini ML, Peccini F, Motolese M, et al. . Comparative evaluation of cardioselectivity of metoprolol OROS and atenolol: a double-blind, placebo-controlled crossover study. *Am Heart J*. 1990 120(2):467-72.
159. Thiringer G SN. Interaction of orally administered metoprolol, Practolol and propranolol with isoprenaline in asthmatics. *Eur J Clin Pharmacol*. 1976;10:163-70.
160. Lawrence DS, Sahay JN, Chatterjee SS, Cruickshank JM. beta-Blockers in asthma. *Drugs*. 1983;25(Suppl. 2):232-6.
161. Matthys H, Doshan HD, Ruhle KH, Applin WJ, Braig H, Pohl M. Bronchospasming properties of celiprolol, a new beta 1, alpha 2-blocker, in propranolol-sensitive asthmatic patients. *J Cardiovasc Pharmacol*. 1986;8 Suppl 4:S40-2.
162. Sue DY, Hansen JE, Wasserman K. beta-Adrenergic blockade with pindolol (LB-46) in mild to moderate asthma. *Chest*. 1981 Nov;80(5):537-42.
163. Short PM, Williamson PA, Lipworth BJ. Effects of hydrocortisone on acute beta-adrenoceptor blocker and histamine induced bronchoconstriction. *Br J Clin Pharmacol*. 2012 May;73(5):717-26.
164. Hanania NA, Mannava B, Franklin AE, Lipworth BJ, Williamson PA, Garner WJ, et al. Response to salbutamol in patients with mild asthma treated with nadolol. *Eur Respir J*. 2010 Oct;36(4):963-5.
165. Short PM, Williamson PA, Anderson WJ, Lipworth BJ. Randomized placebo-controlled trial to evaluate chronic dosing effects of propranolol in asthma. *Am J Respir Crit Care Med*. 2013 Jun 15;187(12):1308-14.
166. Friren B, Michaud JE. Safety comparison of topical brinzolamide 1% and timolol 0.5% in patients with asthma or chronic obstructive pulmonary disease. . *Today's Therapeutic Trends* 2004;22(1):69-80.
167. Schoene RB, Abuan T, Ward RL, Beasley CH. Effects of topical betaxolol, timolol, and placebo on pulmonary function in asthmatic bronchitis. *Am J Ophthalmol*. 1984 Jan;97(1):86-92.
168. Badgett RG, Lawrence VA, Cohn SL. Variations in pharmacology of beta-blockers may contribute to heterogeneous results in trials of perioperative beta-blockade. *Anesthesiology*. 2010 Sep;113(3):585-92.
169. Wheeldon NM, McDevitt DG, Lipworth BJ. Selectivity of antagonist and partial agonist activity of celiprolol in normal subjects. *Br J Clin Pharmacol*. 1992 Oct;34(4):337-43.
170. Hauck RW, Schulz C, Emslander HP, Bohm M. Pharmacological actions of the selective and non-selective beta-adrenoceptor antagonists celiprolol, bisoprolol and propranolol on human bronchi. *Br J Pharmacol*. 1994 Nov;113(3):1043-9.
171. Short PM, Williamson PA, Lipworth BJ. Sensitivity of impulse oscillometry and spirometry in beta-blocker induced bronchoconstriction and beta-agonist bronchodilatation in asthma. *Ann Allergy Asthma Immunol*. 2012 Dec;109(6):412-5.
172. Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J Allergy Clin Immunol*. 1979 Dec;64(6 Pt 1):500-6.

173. Rachelefsky GS, Coulson A, Siegel SC, Stiehm ER. Aspirin intolerance in chronic childhood asthma: Detected by oral challenge. *Pediatrics*. 1975 Sep;56(3):443-8.
174. Marquette CH, Saulnier F, Leroy O, Wallaert B, Chopin C, Demarcq JM, et al. Long-term prognosis of near-fatal asthma. A 6-year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for a near-fatal attack of asthma. *Am Rev Respir Dis*. 1992 Jul;146(1):76-81.
175. Vally H, Taylor ML, Thompson PJ. The prevalence of aspirin intolerant asthma (AIA) in Australian asthmatic patients. *Thorax*. 2002 Jul;57(7):569-74.
176. Nizankowska E, Bestynska-Krypel A, Cmiel A, Szczeklik A. Oral and bronchial provocation tests with aspirin for diagnosis of aspirin-induced asthma. *Eur Respir J*. 2000 May;15(5):863-9.
177. Halvorsen S, Andreotti F, ten Berg JM, Cattaneo M, Coccheri S, Marchioli R, et al. Aspirin therapy in primary cardiovascular disease prevention: a position paper of the European Society of Cardiology working group on thrombosis. *J Am Coll Cardiol*. 2014 Jul 22;64(3):319-27.
178. Cuzick J, Thorat MA, Bosetti C, Brown PH, Burn J, Cook NR, et al. Estimates of benefits and harms of prophylactic use of aspirin in the general population. *Ann Oncol*. 2014 Aug 5.
179. Mills EJ, Wu P, Alberman M, Kanters S, Lanus A, Lester R. Low-dose aspirin and cancer mortality: a meta-analysis of randomized trials. *Am J Med*. 2012 Jun;125(6):560-7.
180. Bavbek S, Dursun AB, Dursun E, Eryilmaz A, Misirligil Z. Safety of meloxicam in aspirin-hypersensitive patients with asthma and/or nasal polyps. A challenge-proven study. *Int Arch Allergy Immunol*. 2007;142(1):64-9.
181. Berges-Gimeno MP, Simon RA, Stevenson DD. Early effects of aspirin desensitization treatment in asthmatic patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2003 Mar;90(3):338-41.
182. Celejewska-Wojcik N, Mastalerz L, Wojcik K, Nieckarz R, Januszek R, Hartwich P, et al. Incidence of aspirin hypersensitivity in patients with chronic rhinosinusitis and diagnostic value of urinary leukotriene E4. *Pol Arch Med Wewn*. 2012;122(9):422-7.
183. Christie PE, Tagari P, Ford-Hutchinson AW, Charlesson S, Chee P, Arm JP, et al. Urinary leukotriene E4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am Rev Respir Dis*. 1991 May;143(5 Pt 1):1025-9.
184. Falliers CJ. Acetaminophen and aspirin challenges in subgroups of asthmatics. *J Asthma*. 1983;20 Suppl 1:39-49.
185. Israel E, Fischer AR, Rosenberg MA, Lilly CM, Callery JC, Shapiro J, et al. The pivotal role of 5-lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin. *Am Rev Respir Dis*. 1993 Dec;148(6 Pt 1):1447-51.
186. Kowalski ML, Grzelewska-Rzymowska I, Rozniecki J, Szmidt M. Aspirin tolerance induced in aspirin-sensitive asthmatics. *Allergy*. 1984 Apr;39(3):171-8.

187. Kowalski ML, Grzelewska-Rzymowska I, Szmidt M, Rozniecki J. Bronchial hyperreactivity to histamine in aspirin sensitive asthmatics: relationship to aspirin threshold and effect of aspirin desensitisation. *Thorax*. 1985 Aug;40(8):598-602.
188. Mastalerz L, Sanak M, Kumik J, Gawlewicz-Mrocza A, Celejewska-Wojcik N, Cmiel A, et al. Exhaled Eicosanoids following Bronchial Aspirin Challenge in Asthma Patients with and without Aspirin Hypersensitivity: The Pilot Study. *J Allergy (Cairo)*. 2012;2012:696792.
189. Micheletto C, Tognella S, Guerriero M, Dal Negro R. Nasal and bronchial tolerability of Rofecoxib in patients with aspirin induced asthma. *Eur Ann Allergy Clin Immunol*. 2006 Jan;38(1):10-4.
190. Stevenson DD, Pleskow WW, Simon RA, Mathison DA, Lumry WR, Schatz M, et al. Aspirin-sensitive rhinosinusitis asthma: a double-blind crossover study of treatment with aspirin. *J Allergy Clin Immunol*. 1984 Apr;73(4):500-7.
191. Stevenson DD, Simon RA. Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol*. 2001 Jul;108(1):47-51.
192. Swierczynska M, Nizankowska-Mogilnicka E, Zarychta J, Gielicz A, Szczeklik A. Nasal versus bronchial and nasal response to oral aspirin challenge: Clinical and biochemical differences between patients with aspirin-induced asthma/rhinitis. *J Allergy Clin Immunol*. 2003 Nov;112(5):995-1001.
193. Szczeklik A, Nizankowska E, Bochenek G, Nagraba K, Mejza F, Swierczynska M. Safety of a specific COX-2 inhibitor in aspirin-induced asthma. *Clin Exp Allergy*. 2001 Feb;31(2):219-25.
194. Vedanthan PK, Menon MM, Bell TD, Bergin D. Aspirin and tartrazine oral challenge: incidence of adverse response in chronic childhood asthma. *J Allergy Clin Immunol*. 1977 Jul;60(1):8-13.
195. Woessner KM, Simon RA, Stevenson DD. The safety of celecoxib in patients with aspirin-sensitive asthma. *Arthritis Rheum*. 2002 Aug;46(8):2201-6.
196. Woessner KM, Simon RA, Stevenson DD. Safety of high-dose rofecoxib in patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2004 Oct;93(4):339-44.
197. Delaney JC. The diagnosis of aspirin idiosyncrasy by analgesic challenge. *Clin Allergy*. 1976 Mar;6(2):177-81.
198. Weber RW, Hoffman M, Raine DA, Jr., Nelson HS. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. *J Allergy Clin Immunol*. 1979 Jul;64(1):32-7.
199. Schuh JF, Pereyra JG. Oral acetylsalicylic acid (aspirin) challenge in asthmatic children. *Clin Allergy*. 1979 Jan;9(1):83-8.
200. Bavbek S, Yilmaz I, Celik G, Aydin O, Erkekcol FO, Orman A, et al. Prevalence of aspirin-exacerbated respiratory disease in patients with asthma in Turkey: a cross-sectional survey. *Allergol Immunopathol (Madr)*. 2012 Jul-Aug;40(4):225-30.
201. Eriksson J, Ekerljung L, Bossios A, Bjerg A, Wennergren G, Ronmark E, et al. Aspirin-intolerant asthma in the population: prevalence and important determinants. *Clin Exp Allergy*. 2014 Jun 24.

202. Debley JS, Carter ER, Gibson RL, Rosenfeld M, Redding GJ. The prevalence of ibuprofen-sensitive asthma in children: a randomized controlled bronchoprovocation challenge study. *J Pediatr*. 2005 Aug;147(2):233-8.
203. Samter M, Beers RF, Jr. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann Intern Med*. 1968 May;68(5):975-83.
204. Valero Santiago A, Gonzalez-Morales MA, Marti Guadano E. Tolerance of nimesulide in NSAID intolerant patients. *Allergy*. 2003 Apr;58(4):367-8.
205. Vane SJ. Aspirin and other anti-inflammatory drugs. *Thorax*. 2000 Oct;55 Suppl 2:S3-9.
206. Gierse JK, Koboldt CM, Walker MC, Seibert K, Isakson PC. Kinetic basis for selective inhibition of cyclo-oxygenases. *Biochem J*. 1999 May 1;339 (Pt 3):607-14.
207. Umemoto J, Tsurikisawa N, Nogi S, Iwata K, Oshikata C, Tatsuno S, et al. Selective cyclooxygenase-2 inhibitor cross-reactivity in aspirin-exacerbated respiratory disease. *Allergy Asthma Proc*. 2011 May-Jun;32(3):259-61.
208. Schellenberg RR, Isserow SH. Anaphylactoid reaction to a cyclooxygenase-2 inhibitor in a patient who had a reaction to a cyclooxygenase-1 inhibitor. *N Engl J Med*. 2001 Dec 20;345(25):1856.
209. Booth HP, Prevost AT, Gulliford MC. Validity of smoking prevalence estimates from primary care electronic health records compared with national population survey data for England, 2007 to 2011. *Pharmacoepidemiol Drug Saf*. 2013 Dec;22(12):1357-61.
210. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ*. 2013;346:f2350.
211. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol*. 1999 Aug;28(4):717-22.
212. Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med*. 2010 Mar;103(3):98-106.
213. Office for National Statistics [Internet]. Death registration summary tables - England and Wales. 2013.
<http://www.ons.gov.uk/ons/search/index.html?newquery=asthma+death> (accessed 1 Sep 2014).
214. National Services Scotland [Internet]. Information Services Division. Diagnoses - hospital care. <http://www.isdscotland.org/Health-Topics/Hospital-Care/Diagnoses/> (accessed 1 Sep 2014).
215. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax*. 2002 Oct;57(10):880-4.
216. Medicines and Healthcare Products Regulatory Agency. Immediate withdrawal of rofecoxib (Vioxx/Vioxxacutate).
<http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON1004263> 2004;(accessed 1 Sep 2014).

217. Hamer J, Grandjean T, Melendez L, Sowton GE. EFFECT OF PROPRANOLOL (INDERAL) IN ANGINA PECTORIS: PRELIMINARY REPORT. *Br Med J*. 1964 Sep 19;2(5411):720-3.
218. Woosley RL, Kornhauser D, Smith R, Reece S, Higgins SB, Nies AS, et al. Suppression of chronic ventricular arrhythmias with propranolol. *Circulation*. 1979 Oct;60(4):819-27.
219. Prichard BN, Gillam PM. USE OF PROPRANOLOL (INDERAL) IN TREATMENT OF HYPERTENSION. *Br Med J*. 1964 Sep 19;2(5411):725-7.
220. Thomas M, Bruton A, Moffat M, Cleland J. Asthma and psychological dysfunction. *Prim Care Respir J*. 2011 Sep;20(3):250-6.
221. Goodwin RD, Fergusson DM, Horwood LJ. Asthma and depressive and anxiety disorders among young persons in the community. *Psychol Med*. 2004 Nov;34(8):1465-74.
222. Heaney LG, Conway E, Kelly C, Gamble J. Prevalence of psychiatric morbidity in a difficult asthma population: relationship to asthma outcome. *Respir Med*. 2005 Sep;99(9):1152-9.
223. Wainwright NW, Surtees PG, Wareham NJ, Harrison BD. Psychosocial factors and incident asthma hospital admissions in the EPIC-Norfolk cohort study. *Allergy*. 2007 May;62(5):554-60.
224. Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, et al. Expert consensus document on beta-adrenergic receptor blockers. *Eur Heart J*. 2004 Aug;25(15):1341-62.
225. Basu K, Palmer CN, Tavendale R, Lipworth BJ, Mukhopadhyay S. Adrenergic beta(2)-receptor genotype predisposes to exacerbations in steroid-treated asthmatic patients taking frequent albuterol or salmeterol. *J Allergy Clin Immunol*. 2009 Dec;124(6):1188-94 e3.
226. Nuttall SL, Routledge HC, Kendall MJ. A comparison of the beta1-selectivity of three beta1-selective beta-blockers. *J Clin Pharm Ther*. 2003 Jun;28(3):179-86.
227. Korte JM, Kaila T, Saari KM. Systemic bioavailability and cardiopulmonary effects of 0.5% timolol eyedrops. *Graefes Arch Clin Exp Ophthalmol*. 2002 Jun;240(6):430-5.
228. Short PM, Anderson WJ, Williamson PA, Lipworth BJ. Effects of intravenous and oral beta-blockade in persistent asthmatics controlled on inhaled corticosteroids. *Heart*. 2014 Feb;100(3):219-23.
229. Lin R, Peng H, Nguyen LP, Dudekula NB, Shardonofsky F, Knoll BJ, et al. Changes in beta 2-adrenoceptor and other signaling proteins produced by chronic administration of 'beta-blockers' in a murine asthma model. *Pulm Pharmacol Ther*. 2008;21(1):115-24.
230. Hanania NA, Singh S, El-Wali R, Flashner M, Franklin AE, Garner WJ, et al. The safety and effects of the beta-blocker, nadolol, in mild asthma: an open-label pilot study. *Pulm Pharmacol Ther*. 2008;21(1):134-41.
231. Alobid I, Benitez P, Bernal-Sprekelsen M, Guilemany JM, Picado C, Mullol J. The impact of asthma and aspirin sensitivity on quality of life of patients with nasal polyposis. *Qual Life Res*. 2005 Apr;14(3):789-93.

232. Olsen AM, Fosbol EL, Lindhardsen J, Andersson C, Folke F, Nielsen MB, et al. Cause-specific cardiovascular risk associated with nonsteroidal anti-inflammatory drugs among myocardial infarction patients--a nationwide study. *PLoS One*. 2013;8(1):e54309.
233. Harbord RM, Higgins J.P.T. Meta-regression in Stata. *The Stata Journal*. 2008;8(4):493–519.
234. Farrington CP, Anaya K., Whitaker H.J., Hocine M.N., Douglas I., Smeeth L. Self-Controlled Case Series Analysis with Event-Dependent Observation Periods. *Journal of the American Statistical Association*. 2011;106:417-26.
235. Daniel RM, Cousens SN, De Stavola BL, Kenward MG, Sterne JA. Methods for dealing with time-dependent confounding. *Stat Med*. 2013 Apr 30;32(9):1584-618.
236. Smeeth L, Donnan PT, Cook DG. The use of primary care databases: case-control and case-only designs. *Fam Pract*. 2006 Oct;23(5):597-604.
237. Quint JK, Mullerova H, DiSantostefano RL, Forbes H, Eaton S, Hurst JR, et al. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). *BMJ Open*. 2014;4(7):e005540.

Appendix 1: Search strategies

Appendix 1.1. MEDLINE search strategy for the systematic review of acute beta-blocker exposure in asthma (chapter 3).

Search	Term	Search	Term	
1	adrenergic*.af.	26	Labetalol.af.	48 double-blind.ti,ab.
2	antagonist*.af.	27	Levobunolol.af.	49 (double adj2 blind).ti,ab.
3	block*.af.	28	Metipranolol.af.	50 (controlled adj3 study).ti,ab.
4	beta-receptor*.af.	29	Metoprolol.af.	51 (comparative adj3 study).ti,ab.
5	beta-adrenergic*.af.	30	Nadolol.af.	52 randomized controlled trial.pt.
6	beta-blocker*.af.	31	Oxprenolol.af.	53 controlled clinical trial.pt.
7	1 and 2	32	Penbutolol.af.	54 43 or 44 or 45 or 46 or 47 or 48
8	1 and 3	33	Pindolol.af.	or 49 or 50 or 51 or 52 or 53
9	1 and 4	34	Practolol.af.	55 exp animals/ not humans.sh.
10	3 and 5	35	Propranolol.af.	56 54 not 55
11	1 and 6	36	Sotalol.af.	57 asthma*.af.
12	7 or 8 or 9 or 10 or 11	37	Timolol.af.	58 (bronchial adj3 hyperreactivity*).af.
13	blockader*.af.	38	Esmolol.af.	59 (bronchial adj3 hyper-reactivity*).af.
14	sympatholytic*.af.	39	Carvedilol.af.	60 (bronchial adj3 hyperrespons*).af.
15	Acebutolol.af.	40	Nebivolol.af.	61 (bronchial adj3 hyper-respons*).af.
16	Alprenolol.af.	41	13 or 14 or 15 or 16 or 17 or 18 or 19 or	62 (airway adj3 hyperreactivity*).af.
17	Atenolol.af.		20 or 21 or 22 or 23 or 24 or 25 or 26 or	63 (airway adj3 hyper-reactivity*).af.
18	Betaxolol.af.		27 or 28 or 29 or 30 or 31 or 32 or 33 or	64 (airway adj3 hyperrespons*).af.
19	Bisoprolol.af.		34 or 35 or 36 or 37 or 38 or 39 or 40	65 (airway adj3 hyper-respons*).af.
20	Bupranolol.af.	42	12 or 41	66 'respiratory sounds'.af.
21	Butoxamine.af.	43	placebo*.ti,ab.	67 wheez*.af.
22	Carteolol.af.	44	trial.ti,ab.	68 (reversible adj3 obstruction).af.
23	Celiprolol.af.	45	random*.ti,ab.	69 57 or 58 or 59 or 60 or 61 or 62 or 63
24	Dihydroalprenolol.af.	46	single-blind.ti,ab.	or 64 or 65 or 66 or 67 or 68
25	Iodocyanopindolol.af.	47	(single adj2 blind).ti,ab.	70 42 and 56 and 69

Appendix 1.2. MEDLINE search strategy for the systematic review of prevalence and mean provocative dose in aspirin-exacerbated respiratory disease (chapter 4).

Search Oral Provocation Challenge Tests and Mean Provocative Dose

1	asthma*.af.	49	aspirin-like.ti,ab,sh.
2	(bronchial adj3 hyperreactivity*).af.	50	(aspirin adj2 like).ti,ab,sh.
3	(bronchial adj3 hyper-reactivity*).af.	51	33 and (49 or 50)
4	(bronchial adj3 hyperrespons*).af.	52	nsaid*.ti,ab,sh.
5	(bronchial adj3 hyper-respons*).af.	53	34 or 35 or 39 or/40-42 or/46-48 or 51 or 52
6	(airway adj3 hyperreactivity*).af.	54	inhibitor*.ti,ab,sh.
7	(airway adj3 hyper-reactivity*).af.	55	antagonist*.ti,ab,sh.
8	(airway adj3 hyperrespons*).af.	56	cyclooxygenase*.ti,ab,sh.
9	(airway adj3 hyper-respons*).af.	57	cyclo-oxygenase*.ti,ab,sh.
10	(reversible adj3 obstruction).af.	58	(cyclo adj2 oxygenase*).ti,ab,sh.
11	'respiratory sounds'.af.	59	cox*.ti,ab,sh.
12	wheez*.af.	60	(prostaglandin adj2 synth*).ti,ab,sh.
13	or/1-12	61	(prostaglandin-endoperoxide adj2 synth*).ti,ab,sh.
14	random*.af.	62	54 and (or/56-61)
15	factorial*.af.	63	55 and (or/56-61)
16	crossover*.af.	64	Aspirin.ti,ab,sh.
17	cross-over*.af.	65	Aceclofenac.ti,ab,sh.
18	placebo*.af.	66	acemetacin.ti,ab,sh.
19	(singl* adj blind*).af.	67	Azopropazone.ti,ab,sh.
20	(doubl* adj blind*).af.	68	Celecoxib.ti,ab,sh.
21	single-blind*.af.	69	Dexibuprofen.ti,ab,sh.
22	double-blind*.af.	70	Dexketoprofen.ti,ab,sh.

Search Population Studies

1	"Aspirin-exacerbated respiratory disease".ti,ab,sh
2	"Aspirin exacerbated respiratory disease".ti,ab,sh
3	"Aspirin-sensitive asthma".ti,ab,sh
4	"Aspirin sensitive asthma".ti,ab,sh
5	"Aspirin-induced asthma".ti,ab,sh
6	"Aspirin induced asthma".ti,ab,sh
7	"Aspirin-intolerant asthma".ti,ab,sh
8	"Aspirin intolerant asthma".ti,ab,sh
9	AERD.ti,ab,sh
10	AIA.ti,ab,sh
11	"NSAID-exacerbated respiratory disease".ti,ab,sh
12	"NSAID exacerbated respiratory disease".ti,ab,sh
13	"NSAID -sensitive asthma".ti,ab,sh
14	"NSAID sensitive asthma".ti,ab,sh
15	"NSAID -induced asthma".ti,ab,sh
16	"NSAID induced asthma".ti,ab,sh
17	"NSAID -intolerant asthma".ti,ab,sh
18	"NSAID intolerant asthma".ti,ab,sh
19	or/1-18
20	Prevalence.ti,ab,sh
21	Incidence.ti,ab,sh
22	Frequency.ti,ab,sh

23	assign\$.af.	71	Diclofenac.ti,ab,sh.	23	Occurrence.ti,ab,sh
24	allocat\$.af.	72	Etodolac.ti,ab,sh.	24	or/20-23
25	volunteer\$.af.	73	Etoricoxib.ti,ab,sh.	25	19 and 24
26	randomized controlled trial.pt.	74	Fenbufen.ti,ab,sh.	26	Morbidity.ti,ab,sh
27	controlled clinical trial.pt.	75	Fenoprofen.ti,ab,sh.	27	Hospitalisation.ti,ab,sh
28	or/14-27	76	Flurbiprofen.ti,ab,sh.	28	Hospitalization.ti,ab,sh
29	analgesi*.ti,ab,sh.	77	Ibuprofen.ti,ab,sh.	29	Emergency.ti,ab,sh
30	anti-inflammatory*.ti,ab,sh.	78	Indomethacin.ti,ab,sh.	30	"asthma attack".ti,ab,sh
31	antiinflammator*.ti,ab,sh.	79	Ketorolac.ti,ab,sh.	31	"asthma exacerbation".ti,ab,sh
32	(anti adj2 inflammator*).ti,ab,sh.	80	Ketoprofen.ti,ab,sh.	32	"severity" OR "severe" OR "uncontrolled"
33	agent.ti,ab,sh.	81	Mefenamic acid.ti,ab,sh.	33	or/26-32
34	29 and (30 or 31 or 32)	82	Meloxicam.ti,ab,sh.	34	19 and 33
35	33 and (30 or 31 or 32)	83	Nabumetone.ti,ab,sh.		
36	non-steroidal*.ti,ab,sh.	84	Naproxen.ti,ab,sh.		
37	nonsteroidal*.ti,ab,sh.	85	Parecoxib.ti,ab,sh.		
38	(non adj2 steroidal*).ti,ab,sh.	86	Piroxicam.ti,ab,sh.		
39	36 and (30 or 31 or 32)	87	Rofecoxib.ti,ab,sh.		
40	37 and (30 or 31 or 32)	88	Sulindac.ti,ab,sh.		
41	38 and (30 or 31 or 32)	89	Tenoxicam.ti,ab,sh.		
42	33 and (36 or 37 or 38)	90	Tolfenamic acid.ti,ab,sh.		
43	antirheumatic.ti,ab,sh.	91	Tiaprofenic acid.ti,ab,sh.		
44	anti-rheumatic.ti,ab,sh.	92	Phenylbutazone.ti,ab,sh.		
45	(anti adj2 rheumatic).ti,ab,sh.	93	or/64-92		
46	43 and (or/36-38)	94	53 or 62 or 63 or 93		
47	44 and (or/36-38)	95	13 and 28 and 94		
48	45 and (or/36-38)				

Appendix 1.3. MEDLINE search strategy for the systematic review of acute exposure to selective NSAIDs or COX-2 inhibitors in people with aspirin-exacerbated respiratory disease (chapter 5).

Search	Search type	Search	Search type	Search	
1	asthma*.af.	33	agent.ti,ab,sh.	64	Aspirin.ti,ab,sh.
2	(bronchial adj3 hyperreactivity*).af.	34	29 and (30 or 31 or 32)	65	Aceclofenac.ti,ab,sh.
3	(bronchial adj3 hyper-reactivity*).af.	35	33 and (30 or 31 or 32)	66	acemetacin.ti,ab,sh.
4	(bronchial adj3 hyperrespons*).af.	36	non-steroidal*.ti,ab,sh.	67	Azopropazone.ti,ab,sh.
5	(bronchial adj3 hyper-respons*).af.	37	nonsteroidal*.ti,ab,sh.	68	Celecoxib.ti,ab,sh.
6	(airway adj3 hyperreactivity*).af.	38	(non adj2 steroidal*).ti,ab,sh.	69	Dexibuprofen.ti,ab,sh.
7	(airway adj3 hyper-reactivity*).af.	39	36 and (30 or 31 or 32)	70	Dexketoprofen.ti,ab,sh.
8	(airway adj3 hyperrespons*).af.	40	37 and (30 or 31 or 32)	71	Diclofenac.ti,ab,sh.
9	(airway adj3 hyper-respons*).af.	41	38 and (30 or 31 or 32)	72	Etodolac.ti,ab,sh.
10	(reversible adj3 obstruction).af.	42	33 and (36 or 37 or 38)	73	Etoricoxib.ti,ab,sh.
11	'respiratory sounds'.af.	43	antirheumatic.ti,ab,sh.	74	Fenbufen.ti,ab,sh.
12	wheez*.af.	44	anti-rheumatic.ti,ab,sh.	75	Fenoprofen.ti,ab,sh.
13	or/1-12	45	(anti adj2 rheumatic).ti,ab,sh.	76	Fluribuprofen.ti,ab,sh.
14	random*.af.	46	43 and (36 or 37 or 38)	77	Ibuprofen.ti,ab,sh.
15	factorial*.af.	47	44 and (36 or 37 or 38)	78	Indomethacin.ti,ab,sh.
16	crossover*.af.	48	45 and (36 or 37 or 38)	79	Ketorolac.ti,ab,sh.
17	cross-over*.af.	49	aspirin-like.ti,ab,sh.	80	Ketoprofen.ti,ab,sh.
18	placebo*.af.	50	(aspirin adj2 like).ti,ab,sh.	81	Mefenamic acid.ti,ab,sh.
19	(singl* adj blind*).af.	51	33 and (49 or 50)	82	Meloxicam.ti,ab,sh.
20	(doubl* adj blind*).af.	52	nsaid*.ti,ab,sh.	83	Nabumetone.ti,ab,sh.

21	single-blind*.af.	53	34 or 35 or 39 or 40 or 41 or	84	Naproxen.ti,ab,sh.
22	double-blind*.af.		42 or 46 or 47 or 48 or 51 or 52	85	Parecoxib.ti,ab,sh.
23	assign\$.af.	54	inhibitor*.ti,ab,sh.	86	Piroxicam.ti,ab,sh.
24	allocat\$.af.	55	antagonist*.ti,ab,sh.	87	Rofecoxib.ti,ab,sh.
25	volunteer\$.af.	56	cyclooxygenase*.ti,ab,sh.	88	Sulindac.ti,ab,sh.
26	randomized controlled trial.pt.	57	cyclo-oxygenase*.ti,ab,sh.	89	Tenoxicam.ti,ab,sh.
27	controlled clinical trial.pt.	58	(cyclo adj2 oxygenase*).ti,ab,sh.	90	Tolfenamic acid.ti,ab,sh.
28	or/14-27	59	cox*.ti,ab,sh.	91	Tiaprofenic acid.ti,ab,sh.
29	analgesi*.ti,ab,sh.	60	(prostaglandin adj2 synth*).ti,ab,sh.	92	Phenylbutazone.ti,ab,sh.
30	anti-inflamator*.ti,ab,sh.	61	(prostaglandin-endoperoxide adj2 synth*).ti,ab,sh.	93	or/64-92
31	antiinflammator*.ti,ab,sh.	62	54 and (56 or 57 or 58 or 59 or 60 or 61)	94	53 or 62 or 63 or 93
32	(anti adj2 inflammator*).ti,ab,sh.	63	55 and (56 or 57 or 58 or 59 or 60 or 61)	95	13 and 28 and 94

Appendix 2: Read codes

2.1 Asthma

H33..00,663..11,H333.00,H33z100,H33z011,14B4.00,H330.12,H33..11,H330.11,663V100,663V300,663V000,H331.11,H33z.00,H33zz11,H33z000,9Q21.00,H331.00,H330011,173A.00,H330111,8H2P.00,H330.00,663P.00,663N.00,H330.14,H33z111,663J.00,663j.00,1O2..00,H33z200,663V.00,663V200,H330000,H330.13,H33zz001,H33zz13,H331111,663p.00,663n.00,H33zz12,173c.00,663d.00,663v.00,H330100,H331000,H33z.11,H334.00,1780.00,H331z00,H330z00,H331100,173d.00

ICD10 codes: J45.0,J45.1,J45.8,J45.9,J46,493,493.0,493.1,493.9.

2.2 COPD

H31..00,H310.00,H310000,H310z00,H311.00,H311000,H311100,H311z00,H312.00,H312000,H312011,H312100,H312200,H312z00,H313.00,H31y.00,H31y000,H31y100,H31yz00,H31z.0,H32..00,H320.00,H320000,H320100,H320200,H320300,H320311,H320z00,H321.00,H322.00,H32y.00,H32y000,H32y100,H32y111,H32y200,H32yz00,H32z.00,H3...00,H3...11,H36..00,H37..00,H38..00,H39..00,H3z..00,H3z..11,H3y..00,H3y..11,H3y0.00,H3y1.00.

ICD10 codes: J41,J41.0,J41.1,J41.8,J42,J43,J43.1,J43.2,J43.8,J43.9,J44,J44.0,J44.1,J44.8,J44.9.

2.3 Bronchiectasis

H34..00,H340.00,H341.00,H34z.00

ICD10 codes: J47,J47.0,J47.1,J47.9.

2.4 Restrictive lung disease

H35..00,H350.00,H351.00,H352.00,H352000,H352100,H352z00,H353.00,H354.00,H355.00,H356.00,H357.00,H35y.00,H35y000,H35y100,H35y200,H35y500,H35y600,H35y700,H35y800,H35yz00,H35z.00,H35z000,H35z100,H35zz00

ICD10 codes: J84.1,J84,J84.0,J84.2,J84.3,J84.9,J84.10,J84.11,J84.111,J84.112,J84.113,J84.114,J84.115,J84.116,J84.117,J84.8,J84.89,J61,J60,J62,J63,J64,J65,J66,J67,J68,J69,J70,J62.0,J62.8,J63.0,J63.1,J63.2,J63.3,1.J63.4,J63.5,J63.6,J66.0,J66.1,J66.8,J67.0,J67.1,J67.2,J67.3,J67.4,J67.5,J67.6,J67.7,J67.8,J67.9,J70.0,J70.1,J70.2,J70.3,J70.4.

2.5 Atrial fibrillation and flutter

G573.00,G573000,G573100,G573200,G573300,G573400,G573500,G573z00

2.6 Cardiovascular disease

G30..00,G30..11,G30..12,G30..14,G30..15,G30..16,G30..17,G300.00,G301.00,G301000,G301100,G301z00,302.00,G303.00,G304.00,G305.00,G306.00,G307.00,G307000,G307100,G308.00,G309.00,G30B.00,G30X.00,G30X000,G30y.00,G30y000,G30y100,G30y200,G30yz00,G30z.00,G30..13,G30A.00,G35..00,G350.00,G351.00,G353.00,G35X.00,G38..00,G380.00,G381.00,G384.00,G38z.00,G311.00,G311.11,G311.12,G311.13,G311.14,G311100,G311200,G311500,G311z00,G312.00,G31y.00,G31y000,G31y100,G31y200,G31y300,G31yz00,G3...00,G3...11,G3...12,G3...13,G311300,G311400,G32..00,G32..11,G32..12,G33..00,G330.00,G330000,G330z00,G33z.00,G33z000,G33z100,G33z200,G33z300,G33z400,G33z500,G33z600,G33z700,G33zz00,G340.00,G340.11,G340.12,G340000,G340100,G342.00,G343.00,G344.00,G34y.00,G34y000,G34y100,G34yz00,G34z.00,G34z000,G3z..00.

2.7 Cerebrovascular disease

G63y000,G63y100,G64..00,G64..11,G64..12,
G64..13,G676000,G6W..00,G6X..00,Gyu6300,Gyu6400,Gyu6500,Gyu6600,Gyu6F00,
Gyu6G00,G65..00,G65..12,G65..13,G656.00,G65y.00,G65z.00,G65z100,G65zz00,G65z000

2.8 Peripheral artery disease

G73..00,G73..11,G73..12,G73..13,
G733.00,G73y.00,G73yz00,G73z.00,G73z012,G73zz00,G73z000,G73z011,Gyu7400

2.9 Chronic kidney disease

1Z1..00,1Z10.00,1Z11.00,1Z12.00,1Z13.00,
1Z14.00,1Z15.00,1Z16.00,1Z17.00,1Z17.11,1Z18.00,1Z19.00,1Z19.11,1Z1A.00,1Z1A.11,
1Z1B.00,1Z1B.11,1Z1C.00,1Z1C.11,1Z1D.00,1Z1D.11,1Z1E.00,1Z1E.11,1Z1F.00,1Z1F.11,
1Z1G.00,1Z1G.11,1Z1H.00,1Z1H.11,1Z1J.00,1Z1J.11,1Z1K.00,1Z1K.11,1Z1L.00,1Z1L.11

2.10 Anxiety

E200.00,
E200300,Eu41111,E200400,E200z00,E200500,E200200,Eu41.00,E200000,Eu41211,Eu41000,
Eu60600,Eu40.00,E202.12,Eu41100,Eu41200,Eu34114,Eu05400,Eu41z00,Eu41y00,Eu93100,
Eu41z11,Eu40y00,Eu41y11,Eu93200,E2D0.00,Eu40z00,Eu41112,Eu41300,
Eu41113,Eu93y12,E200111,E202100,E200100,Eu41012,Eu41011,1B1V.00,Eu40012,225J.00

2.11 Heart failure

G58..00,G58..11,G1yz100,662f.00,662g.00,662h.00,662i.00,585f.00,585g.00,G5yy900,
G5yyA00.

2.12 Nasal polyps

7406000,H110.00,H11..00,2D33.00,7402911,H110z00,H11z.00,H11y.11,7402900

2.13 Seropositive arthritis

N040.00,N065z11,N040T00,N047.00,N04X.00,43b9.00,N040200,M160200,N04..00,N040S00,
N040900,N040800,N040100,N040000,N040700,N040B00,N040D00,N040K00,N040F00,
Nyu1G00,N040500,F371200,N040A00,N040600,Nyu1200,N040H00,N040G00,N040L00,
N040C00,N040400,Nyu1100,N040J00